RETINAL ARTERIOLOSCLEROSIS IN AGE, ESSENTIAL HYPERTENSION, AND DIABETES MELLITUS

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FOR OVER A CENTURY ophthalmologists have been peering into the fundus in an attempt to explain and interpret the findings in various diseases. Without doubt the two diseases which have attracted the most attention and produced the greatest variety of opinions have been hypertension and diabetes mellitus. In spite of the voluminous literature which has accumulated, all of us are aware that there are many unanswered questions regarding these two diseases. This thesis will deal with but one facet of the subject, namely, retinal arteriolosclerosis in age, essential hypertension, and diabetes. It is hoped that within these boundaries presentation of certain studies will shed light on some unanswered questions in the over-all vast problems relating to these subjects.

In spite of the number of articles dealing with these subjects there is a great paucity of data, though no lack of opinion. Also, very few correlative or comparative studies have been done and most of these were on autopsy material rather than in living patients. It is hoped that through this study we may form certain concepts regarding correlation of the retinal arteriolar changes with changes elsewhere in the body. Age has been included in this study as there has been a diversity of opinion regarding the significance of age in the production of retinal arteriolosclerosis.

This study has been stimulated by questions such as the following which the author feels have not been satisfactorily answered, or have been answered in opposite ways by different authors. It is felt that the material to be presented will answer or at least shed light upon these questions.

1. Does retinal arteriolosclerosis occur from age alone or must there be an elevated blood pressure to produce it?

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2. If age does produce retinal arteriolosclerosis, is it as severe as may be produced by the hypertensive process in the younger individual?

3. Does diabetes mellitus generate retinal arteriolosclerosis in the absence of high blood pressure or does the retinal arteriolosclerosis proceed *pari passu* with the elevated blood pressure a diabetic often develops?

4. In living patients how do the organic changes in the retinal arterioles in essential hypertension and diabetes correlate with the changes in the kidney arterioles?

5. Does a study of retinal and kidney arterioles on living patients with essential hypertension and diabetes shed any light on the "Goldblatt mechanism" of producing hypertension in these diseases?

6. In living patients with essential hypertension how do the retinal arteriolar changes correlate with arteriolar alterations in other areas of the body?

PERTINENT LITERATURE

With the invention of the ophthalmoscope physicians began to study and classify the retinal changes in various cardiovascular-renal diseases. Liebrich[1] first described retinopathy in Bright's disease. Following this, controversy existed as to whether the lesions in the retina were the result of retinal vascular disease or were initiated by nitrogenous waste products. Leber,[2] Opin and Rochon-Duvigneaud,[3] and Von Graefe and Schweigger[4] defended the latter view, Gowers,[5] Carl,[6] and Gunn[7] held the former view.

It was not until Volhard[8] published his classic paper that the former view became present-day opinion. However, modern knowledge still does not tell us whether the retinal vascular bed constricts and undergoes sclerosis because of a humoral mechanism or as a defense against an elevated pressure. The observation by the author and others[9,10] that retinal vascular changes may be less in the eye on the side of the body having an occluded carotid artery and hence a lower retinal artery pressure would in general favor the blood pressure theory but could be interpreted in favor of a humoral mechanism by assuming that less of the vasoconstricting substance reached the retina on the occluded side. Observations of the retinas in coarctation of the aorta favor the humoral mechanism as these patients may show minimal retinal damage in spite of a high retinal arterial pressure.

Byrom[11] has recently attempted to answer this question by placing a clamp on the renal artery of a rat after extirpation of the opposite kidney. The retinal arterioles narrowed as the blood pressure elevated.

Under general anesthesia when the blood pressure dropped with the clamp still on the renal artery the retinal vessels dilated. This dilation of the retinal vessels did not occur with the passage of a long time, however, indicating perhaps permanent changes in the retinal arterioles. His work favors a direct causal relationship between blood pressure and changes in the retinal arterioles.

Wise,[12] in some interesting observations on venous occlusion, postulated that the retinal arteriolar damage in high blood pressure was due not only to the high blood pressure but to venous stasis as a result of constriction of the veins at the arteriovenous crossings. Hodge and Dollery[13] hypothesize that the elevated blood pressure is primarily responsible for the damage but that a secondary, yet important role, is played by ischemia caused by capillary compression as a result of leakage of material from small arterioles. Imbriglia[14] implicates the blood pressure as the cause of arteriolosclerosis in essential hypertension. Wagener[15] states "that constriction of the retinal arterial tree like that of the cerebral, is caused by the blood pressure itself."

Thus although multiple factors may be operative in the production of retinal changes in essential hypertension it would seem that changes in the arterioles were most closely related to the height of the blood pressure. The etiology underlying an elevated blood pressure is yet another problem. Following the monumental work of Goldblatt, *et al.*[16] on renal ischemia in laboratory animals it has become widely accepted that certain forms of renal disease (glomerulonephritis and polycystic kidneys) produce hypertension through a humoral mechanism. Concerning the essential type of hypertension there has been a considerable difference of opinion. Goldblatt[17,18] has maintained that all hypertension has as its basis a renal ischemia and that in essential hypertension it is a renal ischemia brought on most usually by renal arteriolosclerosis but occasionally by sclerosis of the larger renal vessels. Scott[19] agrees with Goldblatt. The majority do not share this view but rather believe that arteriolosclerosis in the kidney is not the cause of the hypertension but a process independent of the hypertension and enhanced by the hypertension. In the later stages of the disease the hypertension may finally be aggravated by the renal arteriolosclerosis. Bell,[20] Kimmelstiel and Wilson,[21] and Evelyn[22] hold to this view.

It is well known that the diabetic is prone to hypertension but very little attention has been paid to the arteriolosclerotic changes in the diabetic retina as the more dramatic retinopathy seen does not seem to be the result of arteriolar changes. The reader is referred to the works of Ballantyne[23] and Ballantyne and Loewenstein[24] and Ashton[25]

for comprehensive reviews of diabetic retinopathy. It is hoped that the present studies will bring out the possible relationship of the Goldblatt mechanism to the etiology of hypertension in both essential hypertension and diabetes mellitus.

With respect to whether there is a closer association between age and retinal arteriolosclerosis or hypertension and arteriolosclerosis there is no unanimity of opinion. Koyanagi[26] stated flatly that retinal arteriolosclerosis is invariably preceded by hypertension. Friedenwald[27] in 1935 said that retinal arteriolosclerosis does not occur in generalized sclerosis seen in elderly individuals in which atheromatous lesions are the most common findings. Again in 1947,[28] he referred to arteriolosclerosis as the result of hypertension. Scheie[29,30] believes that the severity of the arteriolosclerosis is in direct relation to the duration and level of the hypertension and does not mention age as a factor. Bedell[31] stated that copper and silver wire arterioles were distinctively hypertensive.

Imbriglia,[14] as previously noted, although not discussing the retinal vessels, states that arteriolosclerosis is the product of high blood pressure. Similarly Morlock,[32] in studying the arterioles of the pancreas, liver, gastrointestinal tract, and spleen, found thickening of the walls only in high blood pressure and not in aged individuals with normal blood pressure.

Other authors feel that age may be associated with as severe a degree of sclerosis of the retinal vessels as is hypertension. Bechgaard and Vogelius[33] and Bechgaard, *et al.*[34] found no difference in retinal vessel changes in young hypertensives and in elderly individuals with a blood pressure below 140/90 mm.Hg. Evelyn, *et al.*[35] imply that age is an important factor in retinal arteriolosclerosis. Kirkendall and Armstrong[36] found in a relatively small group of hypertensives (44) that sclerosis of the retinal arterioles progresses in spite of lowering of the blood pressure. They interpret this as indicative of factors other than high blood pressure in the production of sclerosis. Their conclusion must be regarded as of limited value, however, as even when the blood pressure was lowered on their patients it was not lowered to normal. They do not discuss age as a factor in this communication but in another paper[37] indicate that age and diabetes may produce a picture in the retinal vessels identical to that caused by high blood pressure. This conclusion is qualified by the statement that they had not ruled out transient elevations of the blood pressure in the past in their patients.

Seitz[38] in a recent monograph describes one patient with normal

blood pressure who showed great irregularity in the width of the arterial blood column, generalized narrowing of the arterioles, and irregularity in the light reflex. These findings are at variance with the great majority of opinion which would interpret these changes as consistent with hypertension. At autopsy the arterial wall was thickened and its lumen reduced, changes of arteriolosclerosis. Unfortunately, although he says the patient's blood pressure was normal, he gives neither the blood pressure nor the age of the patient, thus confusing somewhat the significance of his findings.

It is therefore apparent that there is considerable difference of opinion as to the relative importance of age and blood pressure in the production of retinal arteriolosclerosis.

Wendland[39] has indicated that previous comparisons of the changes in the various organs have been limited primarily to autopsy material and that eyes have rarely been included in them. Morlock,[32] in an excellent study of hypertensives, examined the arterioles in the pancreas, liver, gastrointestinal tract, and spleen. He concluded that the arteriolar changes were similar in all the organs. He compared the arterioles in similar organs in elderly individuals with no hypertension and found no measurable change in thickness of the arteriolar wall. He concluded that age was not a factor in the production of arteriolosclerosis.

Farber, *et al.*[40] studied skin biopsies from living patients with essential hypertension but did not correlate the changes with the eyes or other organs. In the majority of instances they found sclerosis of the arteriolar walls. About 10 per cent of their patients had normal arterioles, however. In a series of skin biopsies from normotensive individuals only four of 52 patients had any medical hypertrophy of the arterioles and even the youngest hypertensive had a wall : lumen diameter greater than that found in the oldest individual with normal blood pressure. Wagener and Keith[41] did muscle biopsies in a small number of patients with essential hypertension and found that the changes in the muscle arterioles correlated quite well with the severity of the high blood pressure and the fundus changes. Some muscle biopsies were normal however.

Rosenberg[42] found in cerebral arterioles, in autopsy material, a great increase in thickness and narrowing of the lumen in patients with "malignant hypertension." Alpers, *et al.*,[43] in a series of 100 autopsy cases, attempted to correlate organic damage in the retinal vessels with that of the cerebral vessels. He found very little correlation but unfortunately his study is not of value as he did not compare vessels

of like size but rather compared the retinal arterioles with large arteries of the brain. Also, no blood pressures were given.

Castleman and Smithwick[44] in a study somewhat similar to the author's correlated the retinal changes with kidney arteriolosclerosis in essential hypertension. This was done by renal biopsy performed at the time of sympathectomy for hypertension. Unfortunately they did not compare generalized sclerosis of the retinal vessels with sclerosis in the renal arterioles but rather used a grading in the fundus of one to four that encompassed many things (such as retinopathy) besides just the organic changes in the retinal vessels. Thus they were not comparing like changes in the two organs. In spite of this they felt that the correlation between eye and kidney changes was quite good. Of considerable value in proving the reliability of kidney biopsies done in this manner is their finding that biopsies done on both kidneys in 100 patients showed very similar changes.

There have been no previous correlative studies on retinal and renal arterioles in living patients with diabetes mellitus.

Although not a primary subject for study in this paper it is interesting to note that a profound divergence of views exists as to whether or not "spasm" occurs in the retinal arterioles. Mylius[45] first described "spasm" in the retinal vessels. He presents photographs of the retina to document the spasm. However, other interpretations could be made of the photographs. Wagener[15] in a masterful review of the subject concludes: "There seems to be adequate proof also, both clinical and experimental that generalized and focal narrowing of small arteries and arterioles in the brain and in the retina can occur as functional manifestations in persons with blood pressures elevated by any of several causes." The toxemias of pregnancy offer the best evidence of "spasm" of the retinal arterioles. Rucker[46] has demonstrated photographically the disappearance of focal constrictions after delivery in the toxemias of pregnancy. Hallum[47] found the "spastic constriction of the retinal arterioles" the most consistently reliable change in the eyegrounds of patients with the toxemia of pregnancy. Pickering[48] and Hill and Dollery[49] do not believe that "spasm" in the retinal arterioles exists but that the areas of focal narrowing are organic. Bell[50] finds it hard to accept the thesis that functional constriction of the retinal arterioles can exist.

Essential hypertension is not as satisfactory a disease for the observation of spastic contractions of the retinal arterioles as is toxemia of pregnancy. By its very nature, it is a disease of long duration and usually gradual in onset so that most of the localized constrictions one

observes in essential hypertension are probably organic in nature. Yet Hollenhorst and Wagener[51] found an improvement in focal constrictions of the retinal arterioles following sympathectomy. Adler,[52] however, wrote: "This term [spasm] is only justifiable strictly speaking when one has had the opportunity of seeing the constriction of the vessel disappear. This has never been the case in essential hypertension in my experience. The narrowing either localized or generalized of the retinal artery persists throughout the period of observation of the patient. The only cases in which I consider it justified to use the term 'spasm' are cases of late toxemia of pregnancy, where it is common to find one or more constricted arteries regain their normal caliber after delivery." The author has observed in some of the patients undergoing sympathectomy, and reported in this series, a gradual improvement over weeks and months of both localized and generalized constriction of the retinal arterioles. An organic change might conceivably be gradually altered, however. If we wish to use a term for a non-organic constriction of the retinal arterioles, "increased tonus" would probably be much better than spasm.

DEFINITIONS OF STRUCTURES AND STRUCTURAL ALTERATIONS STUDIED

It is the intent of this study to deal with the finding of generalized arteriolosclerosis of the retinal vessels as it relates to age, essential hypertension, and diabetes mellitus and to correlate these organic retinal arteriolar changes with those in the renal arterioles in living patients with essential hypertension and diabetes. Further correlative material is also presented with respect to hypertension as it pertains to the skin, omentum, and muscle. It will be noted that we refer to the retinal "arteries" as arterioles. These vessels satisfy the arteriole definition on two counts. First, they are of the proper size varying between 63 and 134 microns at the edge of the disc.[53] According to Maximow and Bloom[54] arterioles are those arteries smaller than 300 microns. Secondly, they fit structurally the definition of an arteriole. Friedenwald[27] defines an arteriole as one without an internal elastic lamina or a continuous muscular coat. All arteries except those on or near the disc are arterioles according to this definition also. Scheie,[30] Wise,[12] Snell,[55] Cogan,[56] and Harry and Ashton[57] accept the view that the retinal "arteries" should be considered arterioles. The smaller branches of the retinal arterioles are about the size of the efferent renal arterioles. The larger retinal arteries correspond more to the size of the afferent renal arterioles.

For a study of this nature we must also have evidence that what we describe with the ophthalmoscope as sclerosis of the retinal arterioles is indeed an organic change. The author believes this has been conclusively demonstrated. Greear[58] in an excellent comparative ophthalmoscopic-pathologic study found that the degree of sclerosis (medial hypertrophy and hyalinization) seen microscopically paralleled the degree of sclerosis seen ophthalmoscopically. The arteriovenous crossing phenomena which we recognize as sclerosis are the result of the degenerative process affecting a common vein-artery adventitial coat. This was first pointed out by Koyanagi[26] and recently re-emphasized by Seitz.[38] Friedenwald[28] separated the atherosclerotic process in the retinal vessels from the arteriolosclerotic process. The former may occur only near the disc and produces an area of focal constriction which is usually asymmetrical. The latter produces the typical changes we recognize with the ophthalmoscope as arteriolosclerosis and it is with these that we are concerned. These changes may be seen in some eyes with a microscope in the living individual by using a slit-beam and focussing near the arteriole, thereby creating an indirect lateral illumination of the arteriole. The wall will appear as a thickened cylinder. Pathologically, they consist of a thickening of the arteriolar wall and an increase in the wall to lumen diameter brought about by replacement of the normal wall with collagenous fibers which, with the passage of time, undergo hyalinization. In arterioles possessing a muscular coat there may be in the early stages a hypertrophy of the muscle fibers but they are later replaced by collagenous tissue.

Bell's classification of renal arteriolosclerosis was used for grading the renal arterioles. It extends from grade 0 (normal) through grade IV (complete occlusion). Grades I, II, and III are equivalent to mild, moderate, and severe arteriolosclerosis. An illustration of grade II renal arteriolosclerosis is shown in Figure 1. Grade IV was not encountered in this study of living patients. Bell's classification was selected because the divisions given in his grading are the same in number, ranging from normal to complete occlusion, as the grading used for the retinal arterioles and hence comparable steps are involved.

For grading the generalized sclerosis of the retinal arterioles, the grading recommended by the Committee on Classification of Hypertensive Disease of the Retina of the American Ophthalmological Society[59] was used. It is reproduced in Table 1. The author feels that this is by far the best system yet devised as it can be reproduced by different well-trained observers. Evelyn[22] has also found that a grading

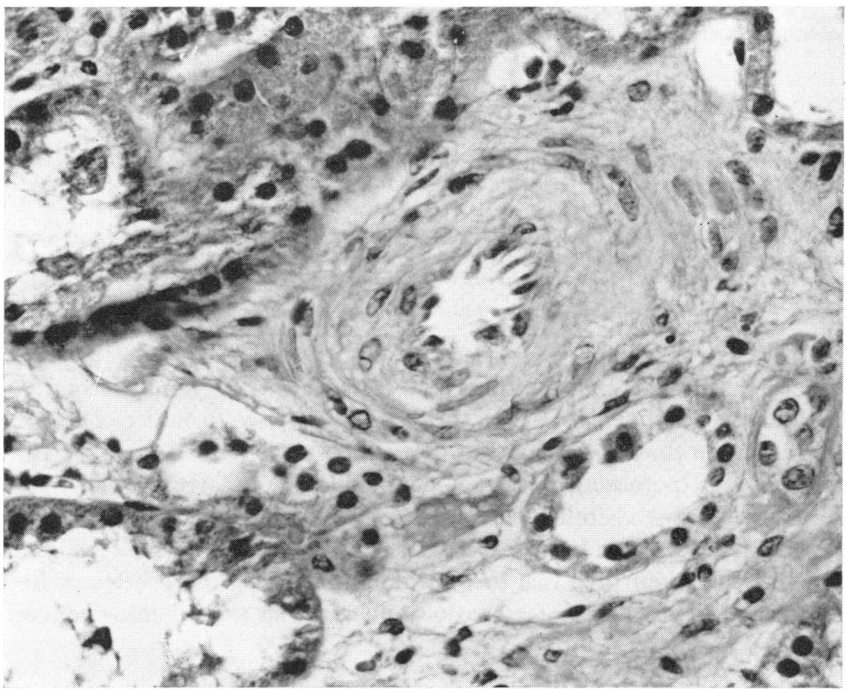

FIGURE 1
Photograph of a renal arteriole showing grade II arteriolosclerosis from a biopsy in a patient with essential hypertension. × 250

similar to this has a high degree of reproducibility by different observers. Scheie[29,30] used essentially this grading also. Generalized narrowing and focal narrowing of the arterioles was also graded according to the Committee's recommendations but is not pertinent to this study and therefore is not included in the data.

Widening and brightening of the light reflex in retinal arteriolosclerosis are interesting phenomena and deserve a brief explanation. These manifestations can only be caused by a greater percentage of the reflex coming from the vessel wall than from the blood column, the reverse of the normal case. The reflex is wider because a radius of curvature which is greater gives a wider reflected image or a wider zone of specular reflection. It is brighter because there must be a greater change in index of refraction between vitreous and vessel wall in the sclerotic vessel than there is in the normal. This is an application of one of the laws of optics which states that the percentage of light

TABLE 1. GRADING OF GENERALIZED SCLEROSIS OF THE RETINAL ARTERIOLES RECOMMENDED BY THE COMMITTEE ON CLASSIFICATION OF HYPERTENSIVE DISEASE OF THE RETINA OF THE AMERICAN OPHTHALMOLOGICAL SOCIETY

Grade I, widening and increased brightness of the light reflex, *slight depression of the veins at av crossings*, with reduction in visibility of the underlying veins
Grade II, copper color to arterioles, *definite depression of veins at av crossings*, widening of av crossings, and *almost complete invisibility of the veins* where they lie beneath the arterioles
Grade III, silver color to arterioles, depression of veins at av crossings and *distal dilatation of the veins*, widening of av crossings, right-angled av crossings and *complete invisibility of those portions of the veins* which underlie the crossing arterioles
Grade IV, arterioles visible only as white fibrous cords without blood column

reflected as light passes from one transparent or semi-transparent medium to another varies directly as the difference in index of refraction between the two media. This is an agreement with Wilmer, *et al.*[60] and Gans.[61] Increasing optical heterogeneity of the vessel wall leads to its increasing visibility as sclerosis progresses. The overlay of the heightened reflex and decreased transparency of the vessel wall on the blood column give rise to the familiar "copper" and "silver wire" arterioles.[62] This optical explanation thus matches the organic changes.

METHOD OF INVESTIGATION

The fundi of a total of 1190 patients were examined. Of these 973 were either normotensive or had essential hypertension and were non-diabetics. Of the hypertensives in this group, 85 had sympathectomy because of hypertension. On this group a varying number of kidney, omental, skin, and muscle biopsies were performed. The remainder of this group (888) was used for the comparison of the effects of age and hypertension upon the retinal vessels. They were not divided simply into normotensives and hypertensives but rather into various blood pressure and age groups.

Of the total of 1190 patients, 217 were diabetics. The degree of retinal arteriolosclerosis in these 217 was compared with a group of 217 chosen from the non-diabetics. To eliminate the factors of age and blood pressure each group had the same average age and blood pressure. Average age was 55 and average blood pressure was 80 mm.Hg. The youngest diabetic was 16 and the oldest 84. The youngest of the non-diabetics was 6 and the oldest 88. The lowest and highest diastolic blood pressures of the diabetics were 50 and 120 mm.Hg. For the selected group of 217 non-diabetics, the low and high diastolic blood pressures were 55 and 134. Age and blood pressures were scat-

tered evenly over a wide range but the average age and blood pressure was the same.

Of the 217 diabetics, 20 had renal biopsies done which were considered adequate for study of the arterioles of the kidney. The neurosurgeon who performed the sympathectomy for hypertension was more willing to do a renal biopsy than to include omentum, skin, and muscle biopsies. Omental biopsy was somewhat of an added hazard because the surgeon had to perforate the peritoneum to obtain it and thereby theoretically added additional danger of infection. However, no complications occurred. Hence 85 kidney biopsies were done but only 20 omental, 22 skin, and 22 muscle biopsies. The renal biopsies averaged 5 by 5 by 10 mm. in size. The omental biopsies averaged 5 by 10 by 20 mm. in size. The skin biopsies averaged 5 by 5 by 10 in. size. The muscle biopsies averaged 10 by 10 by 30 mm. in size.

Renal biopsy in the diabetics was done with a 14-gauge Franklin modification of the Vim-Silverman needle. The technique has been well outlined by Arnold and Spargo[63] and Newell, *et al.*[64] Renal biopsy is not without risks, the main one being hemorrhage severe enough to warrant transfusing or operative interference. Only one patient suffered severe enough hemorrhage to necessitate transfusion. The patients were admitted to the hospital for 48 hours.* Needle biopsies contain from 5 to 30 glomeruli with their arterioles whereas the surgical biopsies in hypertensives, being larger, contained more glomeruli, usually 50 or more. All biopsy specimens were stained with hematoxylin and eosin. The pathologist graded the degree of renal arteriolosclerosis in both the diabetics and the hypertensives without knowledge of the eye findings.

The majority of the retinas were examined by the author although some were seen by senior residents who had been thoroughly trained in the Committee's classification. Repeated checks by the author indicated repeatability of the observations. This has already been demonstrated by Evelyn.[35] No bias was evident.

Blood pressure readings were the average of at least two or more readings in the sitting position. Although a systolic average was recorded, only the diastolic level was used for this study as it was the most constant and is generally considered to be most indicative of arteriolar stress. The data accumulated by the studies were analyzed with emphasis on the comparative influence of age, hypertension, and

*The author is indebted to Dr. Frederic Goetz of the Department of Medicine of the University of Minnesota for the performance of the renal biopsies in the diabetics.

diabetes on generalized sclerosis of the retinal arterioles. Also, a comparison of the retinal arterioles with the renal arterioles of both the diabetic and the hypertensive patients was made. In the hypertensive patient a comparison was also made with the omental, skin, and muscle arterioles.

In most cases an attempt was made to learn the duration of the hypertension and diabetes but, particularly in the case of hypertension, these figures can be very unreliable. They are not included in the study.

Except for the diabetic patients with hypertension, only patients with essential hypertension were studied. No toxemias of pregnancy were included. Patients with extensive retinal disease from local causes (for example, retinitis pigmentosa) were also excluded, as were those with pernicious anemia, lupus erythematosus, and other systemic diseases.

RESULTS

The results are summarized in Tables 2 through 7. With the exception of Table 5, actual numbers of cases are given; Table 5 is expressed

TABLE 2. NON-DIABETIC PATIENTS OF VARIOUS AGES ARRANGED ACCORDING TO AGE AND BLOOD PRESSURE

Age	Diastolic blood pressure (mm. Hg)	Grade of generalized sclerosis in retinal arterioles					Totals
		0	I	II	III	IV	
Under 30	Under 70	18					18
	70–85	53					53
	85–100	11					11
	100–110	1		1			2
	Over 110	2					2
30–45	Under 70	13					13
	70–85	61					61
	85–100	19	5				24
	100–110	4	14	7	2		27
	Over 110	7	17	25	5		54
45–60	Under 70	10					10
	70–85	107	13				120
	85–110	46	25	1			72
	100–110	7	21	4			32
	Over 110	10	10	10	2	1	33
Over 60	Under 70	65	3				68
	70–85	95	22	1			118
	85–100	55	38	27			120
	100–110	8	15	8	1		32
	Over 110		8	8	1		17
TOTALS		592	191	92	11	1	888
	Kidney biopsies on patients with essential hypertension						85
						TOTAL	973

TABLE 3. PATIENTS WITH DIABETES MELLITUS ARRANGED ACCORDING TO AGE AND BLOOD PRESSURE

Age	Diastolic blood pressure (mm. Hg)	Grade of generalized sclerosis in retinal arterioles					Totals
		0	I	II	III	IV	
Under 30	Under 70	4					4
	70–85	11	1				12
	85–100	4					4
	100–110			3			3
	Over 110	1	2				3
30–45	Under 70	4					4
	70–85	10	4	3			17
	85–100	3	1	1			5
	100–110			3			3
45–60	Under 70	5					5
	70–85	19	7	3			29
	85–100	9	8	3			20
	100–110	1	1	2	1		5
Over 60	Under 70	13	4	2			19
	70–85	34	13	3			50
	85–100	13	9	6	1		29
	Over 100		3	2			5
TOTALS		131	53	31	2		217

TABLE 4. 217 NON-DIABETICS HAVING THE SAME AVERAGE AGE AND BLOOD PRESSURE AS THE 217 DIABETICS IN TABLE 3. (ONE MAY COMPARE THE NUMBER OF CASES SHOWING VARIOUS GRADES OF SCLEROSIS IN THE TWO GROUPS.)

Age	Diastolic blood pressure (mm. Hg)	Grade of generalized sclerosis in retinal arterioles					Totals
		0	I	II	III	IV	
Under 30	Under 70	4					4
	70–85	12					12
	85–100	7					7
	Over 100	2		1			3
30–45	Under 70	4					4
	70–85	17					17
	85–100	5					5
	Over 100	1	2				3
45–60	Under 70	5					5
	70–85	18	12				30
	85–100	20					20
	Over 100		4	1			5
Over 60	Under 70	17	1				18
	70–85	29	20	1			50
	85–100	29					29
	Over 100	1	4				5
TOTALS		171	43	3			217

TABLE 5. PERCENTAGE OF NON-DIABETIC AND DIABETIC PATIENTS HAVING THE SAME AVERAGE AGE AND BLOOD PRESSURE SHOWING VARIOUS GRADES OF SCLEROSIS OF RETINAL ARTERIOLES

	Grades of sclerosis					All grades of sclerosis
	0	1	II	III	IV	
217 non-diabetics	78	21	1	0	0	22
217 diabetics	60	24	15	1	0	40

in percentage of total number of patients. For ease of interpretation the material in Tables 2 and 3 is presented in graph form in Figures 2 and 3 with the number of cases expressed in terms of percentage of total patients showing each degree of sclerosis. The data in Table 6 are reproduced in graph form in Figure 4. Percentages upon which conclusions are based have been subjected to statistical analysis.*†

It is statistically reliable that patients over 60 years of age without diabetes and with a diastolic blood pressure under 85 mm.Hg have less than a one per cent chance of having more than grade I sclerosis. Eighty-three per cent of the patients under 45 years of age with a diastolic blood pressure over 100 mm.Hg show some degree of sclerosis and 45 per cent of these same patients show greater than grade I sclerosis. Yet of patients over 60 years of age and with a diastolic blood pressure under 70 mm.Hg, only 5 per cent will show any degree of sclerosis of the retinal arterioles and none will show more than grade I. The relationship of age and blood pressure is seen plainly in Table 2 and Figure 2. These are of course non-diabetics.

In comparing the degree of retinal arteriolosclerosis in the diabetic and non-diabetic, a greater percentage of diabetics showed sclerosis than did non-diabetics (Figures 2 and 3). However, the average diastolic blood pressure of all the non-diabetics was 87 mm.Hg, whereas the average of all the diabetics was 80 mm.Hg. This does not mean

*The author is indebted to Dr. Harriet Kelly, statistician of the Area Medical Office, Veterans Administration, Minneapolis, Minnesota, who did the statistical analyses.

†The following formula was used for determining the statistical significance of certain relationships discussed in the paper:

$$K = \frac{bc - ad - n_1 + n_2}{2} \frac{n_1 + n_2}{n_1 n_2 (a + c)(b + d)}$$

where K = standardized normal variable; a = number of occurrences in first sample; b = number of non-occurrences in first sample; c = number of occurrences in second sample; d = number of non-occurrences in second sample; n_1, n_2 = size of first and second samples, respectively.

TABLE 6. COMPARISON OF DEGREE OF ARTERIOLOSCLEROSIS IN RETINA AND KIDNEY OF DIABETIC PATIENTS AND PATIENTS WITH ESSENTIAL HYPERTENSION WITHOUT DIABETES*

Grade kidney	Grade in retina 0	1	II	III	IV	Totals
A. Essential hypertensive patients without diabetes (patients with essential hypertension who had kidney biopsy performed at the time of sympathectomy for hypertension)						
0	6	13	8	1		28
I		14	9	2		25
II		11	15	1		27
III			2	3		
IV						
TOTALS	6	38	34	7		85
B. Diabetic patients (patients upon whom a needle biopsy of the kidney was performed)						
0	4	1				5
I	4	1	1			6
II		2	3			5
III			3	1		4
IV						
TOTALS	8	4	7	1		20

*The grade in both A and B refers to the degree of arteriolosclerosis observed in the kidney and the retina.

TABLE 7. PATIENTS WITH ESSENTIAL HYPERTENSION AND NO DIABETES WHO HAD BIOPSIES PERFORMED UPON THE OMENTUM, SKIN, AND MUSCLE AT THE TIME OF SYMPATHECTOMY FOR THEIR HYPERTENSION

	Grade in retina 0	1	II	III	IV	Totals
Grade in omentum						
0		11	4			15
I			2			2
II			3			3
III						
IV						
TOTALS		11	9			20
Grade in skin						
0		14	6			20
I						
II			2			2
III						
IV						
TOTALS		14	8			22
Grade in muscle						
0		10	6			16
I		1	2			3
II			2			2
III			1			1
IV						
TOTALS		11	11			22

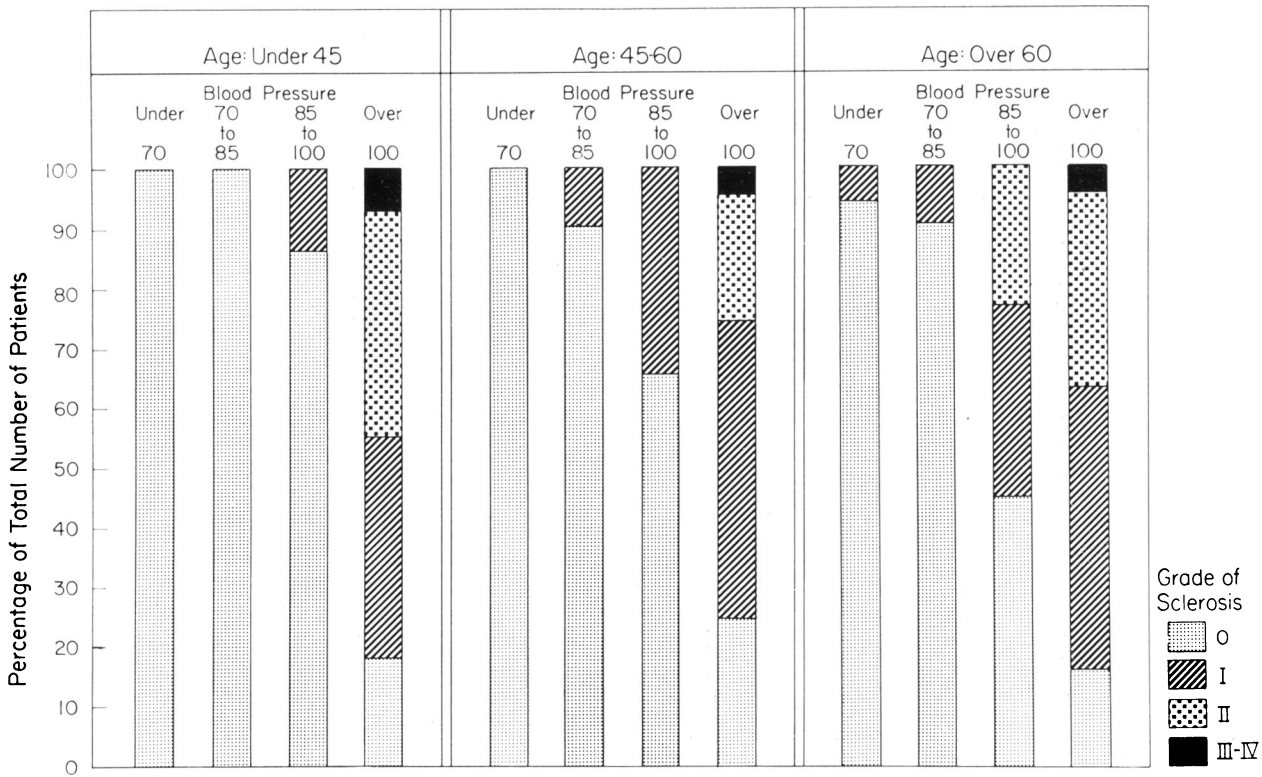

FIGURE 2.

Percentages of non-diabetic patients showing various degrees of retinal arteriolosclerosis. Patients are arranged according to age and blood pressure. All blood pressures are diastolic and in mm.Hg.

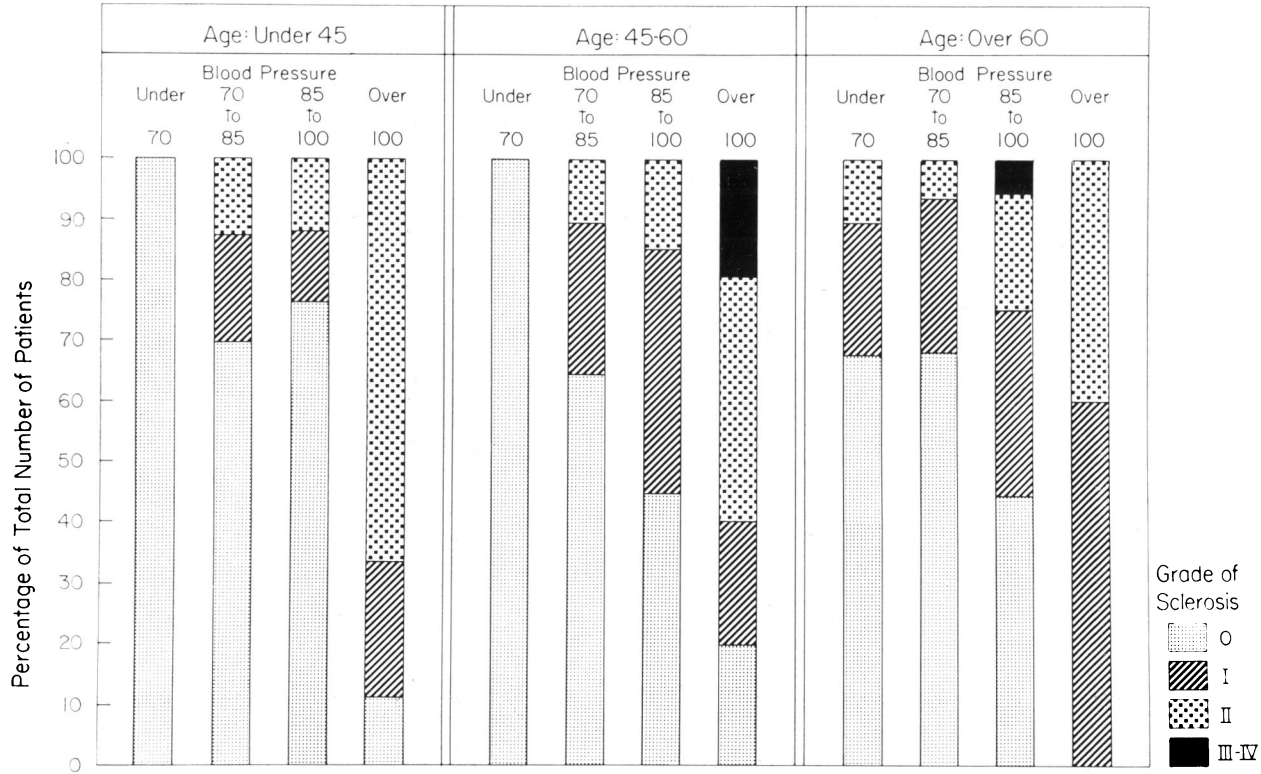

FIGURE 3.

Percentages of diabetic patients showing various degrees of retinal arteriolosclerosis. Patients arranged according to age and blood pressure. All blood pressures are diastolic and in mm.Hg.

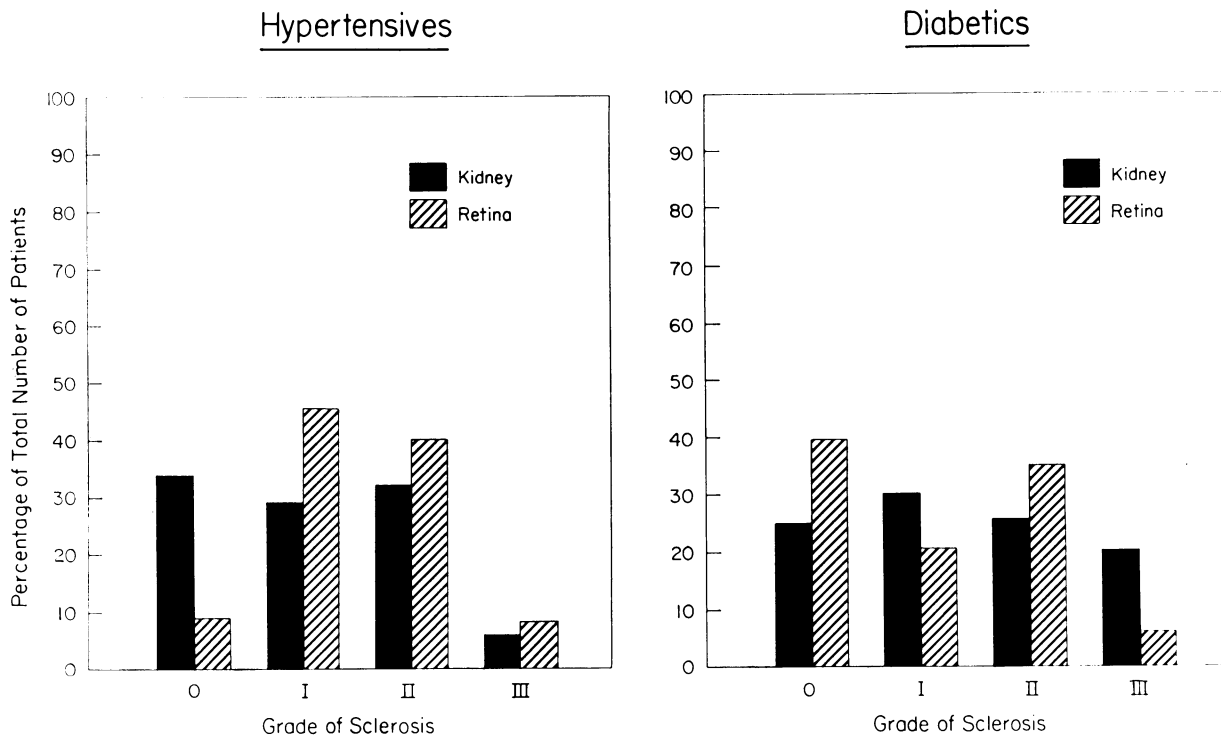

FIGURE 4

Hypertensives and diabetics compared with respect to percentage of cases showing various degrees of arteriolosclerosis in the retina and kidney. Data are derived from Table 6. The figure is interesting because the number of normal kidneys exceeds the number of normal retinas in hypertensives yet the reverse is true in the diabetics. The significance of this in relation to the Goldblatt mechanism is discussed in the text.

diabetics have lower blood pressures than non-diabetics (the reverse is probably true) but simply that many severe essential hypertensives were present in the non-diabetics. As previously indicated, to eliminate blood pressure and age as a factor in comparing the effect of diabetes on sclerosis of the retinal arterioles, a group of 217 non-diabetics was selected which had an average diastolic blood pressure of 80 mm.Hg and an average age of 55, the same as the average age of the diabetic group. In comparing these two groups the preponderance of sclerosis in the retinal arterioles in the diabetic was evident. (Compare Tables 3 and 4. Also note Table 5 where the two groups are compared with respect to the percentages of each group showing various grades of sclerosis. These percentages are statistically reliable.)

In comparing the changes in the retinal arterioles with changes elsewhere in the body it is interesting to note that of the non-diabetic hypertensives, 28 kidneys showed no sclerosis, yet 22 of these cases had grade I or more sclerosis of the retinal arterioles (Table 6). However 87 per cent of eyes and kidneys differed by not more than one grade. In the kidneys from the diabetics there was not this tendency for detectable retinal arteriolosclerosis to precede the renal changes. In fact the reverse was true to a slight degree (Table 6 and Figure 4). The scleroses in the two organs paralleled each other very closely. These findings shall be further considered under the discussion. In hypertensives the retinal arterioles appear to be more readily affected than the arterioles in skin, omentum, and muscle (Table 7).

DISCUSSION

Wagener[53] stated "Whether or not the ophthalmoscopic signs of retinal arteriolosclerosis are to be interpreted as always indicative of hypertension is debatable." Our results in a study of non-diabetic individuals at various ages and with various blood pressures indicate that retinal arteriolosclerosis may be interpreted as usually indicative of hypertension. Our findings indicate that high blood pressure is far more closely associated with generalized organic retinal arteriolar changes than is age. They are thus more consistent with the views of Koyanagi,[26] Friedenwald,[28] Bedell,[31] Scheie,[30] Salus,[65] and Biro[66] and at variance with the opinions of Bechgaard and Vogelius,[33] Bechgaard, *et al.*,[34] Seitz,[38] Sautter,[67] Behrendt,[68] Leishman,[69] Davis and Landau,[70] and Larsen[71] who ascribed to age a role almost as important as high blood pressure in evolving the changes of retinal arteriolosclerosis.

Perhaps one important reason for the differences of opinion which

have arisen over the years is that there is probably no unanimity of opinion on just what is a "normal" blood pressure for any particular age group. Studies often accept a diastolic blood pressure under 90 mm.Hg as normal in the older individuals and if this criterion is accepted as indicative of a "normal" blood pressure more retinal arteriolosclerosis will be found in older individuals with "normal" blood pressures. With this standard as a normal, the data presented indicate that retinal arteriolosclerosis is a process independent of hypertension occurring with age alone but vastly enhanced by hypertension. If a "normal" diastolic of under 70 mm.Hg is the standard, age is associated still less with retinal arteriolosclerosis. Only 5 per cent of patients over 60 with a diastolic blood pressure under 70 mm.Hg had grade I sclerosis and none had more than grade I. It is almost as though there would be no retinal arteriolosclerosis if the blood pressure could be made low enough throughout the person's lifetime. It is interesting to note that the Society of Actuaries[72] and Kannel, *et al.*[73] found that even the slightest sustained elevation of the diastolic pressure will shorten a person's longevity. Our findings are consistent with the theory that the elevated blood pressure causes the arteriolar changes.[74] This does not mean that they may be offered as proof of this belief, however, as it is possible that some underlying etiologic mechanism, neural or hormonal, is producing both high blood pressure and arteriolar damage in a parallel degree. However, the widely held opinion, so well expressed by Perry,[75] that reduction of blood pressure by any means prolongs the life of the individual with hypertension would seem to indite the pressure itself as a cause of the damage in the vessels.

Whatever the underlying theories, the inescapable conclusion is that in non-diabetics, regardless of the age of the individual, as the blood pressure increases, the degree of retinal arteriolosclerosis increases. Minimal sclerosis may apparently occur in some individuals without an elevated pressure as age advances, however.

When one compares the diabetics with the non-diabetics our data support the belief that diabetes does enhance the arteriolosclerotic process in the retina without the presence of hypertension (Table 5). White and Waskow[76] and Heinsius[77] have also reported retinal arteriolosclerosis in diabetics without hypertension.

No attempt was made to correlate the relationship of the duration of the high blood pressure in non-diabetics to the degree of retinal arteriolosclerosis because it is almost impossible to accurately determine the time of onset of the high blood pressure in a given patient.

The method that has been used to compare the degree of retinal arteriolosclerosis with changes elsewhere in the body might be criticized on two counts. First, it might be said that it is not valid to compare the degree of sclerosis observed with the ophthalmoscope with that observed with the microscope. However, as we have already shown, the same process is being observed in the different locations and our grading runs the gamut from the normal to severe in each case. Obviously, the more sharply the dividing lines are drawn, the more chance there is in individual cases for human errors of judgement to occur because nature does not draw sharp dividing lines. Also it must be remembered that we are dealing with biological correlations and not correlations of equations of mathematical preciseness. Correlations are statistical, however, and biologic correlations of this nature must often form the basis of clinical judgement. A second objection might be that the biopsy method does not provide an adequate sample. Castleman and Smithwick[78] have proved that kidney biopsies done at the time of sympathectomy for hypertension are an adequate sample. In the case of the needle biopsy, the criticism might be valid as the biopsy is smaller. However, this does not seem likely as the correlation between the diabetic kidney and the eye changes is close.

In comparing early changes in the eye and the kidney in nondiabetic hypertensives it will be seen (Table 6) that 28 kidneys showed no sclerosis yet the retinal arterioles in 22 of these cases had grade I or more organic changes. When one considers that those patients had hypertension severe enough to be associated with organic changes in their retinal arterioles it seems unwise to conclude as Goldblatt[17,18,79] does that essential hypertension is produced by organic renal arteriolar changes. Our findings do not support the "Goldblatt mechanism" in essential hypertension. Organic changes in the large renal vessels as a cause of essential hypertension also seem remote.[80]

In general, renal and retinal arteriolosclerosis in hypertensives correlate well, the sclerosis in 87 per cent of kidneys and eyes differing by not more than one grade. If a tendency exists it is for the sclerosis to be detectable in the retina before it is in the kidney.

With respect to the diabetic patients the situation is somewhat different. Of the five patients which showed normal renal arterioles only one retina presented any arteriolosclerosis. Yet of eight patients with normal eyes, four showed organic renal arteriolar changes. All of the twenty cases showed either equal changes in the retinas and kidneys or changes differing by not more than one grade. There is not the

tendency for retinal arteriolosclerosis to manifest itself without the kidney showing renal arteriolosclerosis as well. These findings are certainly consistent with a "Goldblatt mechanism" as a cause of hypertension in the diabetic. Further evidence of renal arteriolosclerosis antedating hypertension in the diabetic is the observation of definite renal arteriolosclerosis in three patients ages 20, 21, and 35 with diastolic blood pressures of 70, 50, and 80 mm.Hg. We may conceive in the diabetic a hypertension produced through renal arteriolosclerosis. In essential hypertension the elevated blood pressure probably comes first with renal arteriolosclerosis secondary to either the hypertension or the agents producing the hypertension. Renal arteriolosclerosis then enhances the hypertension. In both cases a vicious circle is possible.

In comparing changes in the retina in non-diabetic hypertensives with those in the omentum, skin, and muscle, a relationship similar to that of the retina to the kidney is found. There is a trend to recognition of the changes in the retinal arterioles before evidence of changes in the other organs is present. From Table 7 it will be seen that 15 omental, 20 skin, and 16 muscle biopsies showed no arteriolosclerosis yet retinal arteriolosclerosis of some degree was present. Statistical analysis shows that retinal arteriolosclerosis equals or exceeds that found in these three organs. Yet changes in all three organs differed by not more than one grade from the retina in the majority of instances. Eighty per cent of the omental biopsies and 73 per cent of the skin and muscle biopsies differed by not more than one grade from the retina. It will also be noted from Table 7 that the skin, omentum, and muscle rarely showed more than grade II sclerosis. This is in agreement with Fahr[81] and Bell and Clawson.[82] Other observers[83] in studying muscle biopsies found more extensive arteriolosclerotic changes than Fahr or Bell and Clawson.

From the ophthalmological viewpoint the important observation to be made from a study of these three organs and their relationship to the eye is that in a diffuse disease such as essential hypertension, the retinal arteriolosclerotic changes are a sensitive, early indicator of disease in other organs.

SUMMARY AND CONCLUSIONS

A total of 1190 patients was studied. Of these 973 were non-diabetics and 217 diabetics. With these patients a comparison of the effect of age and the hypertensive process upon generalized retinal arteriolo-

sclerosis was made. Only essential hypertension was studied. Within the total group, 85 living patients with essential hypertension had surgical kidney biopsies, 20 had omental biopsies, 22 skin biopsies, and 22 muscle biopsies. Twenty diabetic patients had needle kidney biopsies. The degree of retinal arteriolosclerosis was compared with arteriolosclerosis in these organs.

This study was undertaken in an attempt to answer the questions posed in the introduction. The following conclusions have been drawn and I believe aid in answering these questions.

1. The hypertensive process is far more important than age in producing retinal arteriolosclerosis but mild (grade I) retinal arteriolosclerosis may occur from increased age alone. Most older individuals with low diastolic pressures, however, show no retinal arteriolosclerosis.

2. Diabetes mellitus is capable of enhancing retinal arteriolosclerosis in the absence of hypertension.

3. Studies of the retinal and renal arterioles in the 85 living patients with essential hypertension revealed that 28 showed no renal arteriolosclerosis yet 22 of these showed grade I or more retinal arteriolosclerosis. These findings are not compatible with the theory which holds that renal arteriolosclerosis, through alteration of renal hemodynamics and liberation of a pressor substance, is responsible for essential hypertension. The results are compatible with the belief that renal arteriolosclerosis is the result of the hypertensive process in so-called essential hypertension.

4. Eighty-seven per cent of patients with essential hypertension showed either equal changes or a difference of not more than one grade of sclerosis in the retinal and renal arterioles. This is taken to indicate that correlation of changes in retinal and renal arterioles in hypertension is good and the retinal arterioles are a useful indicator of the status of the renal arterioles.

5. Studies of retinal and renal arterioles in 20 living diabetic patients revealed 100 per cent of the patients showed either equal changes or a difference of not more than one grade in the two organs. This indicates a good correlation of changes in the retinal and renal arterioles in the diabetic. Of eight patients with normal eyes, four showed organic renal arteriolar changes and of the five patients who showed normal renal arterioles only one retina evidenced any arteriolosclerosis. These findings are in contrast to the early changes in essential hypertension (where changes tend to be recognized first in the eye) and are consistent with renal arteriolosclerosis as the primary mechanism of production of hypertension in a diabetic (Goldblatt mechanism).

6. Comparison of retinal arterioles with those of skin, omentum, and muscle in living patients with essential hypertension confirms the diffuse nature of the hypertensive process. Also, retinal arteriolosclerosis in essential hypertension appears to equal or exceed the changes in these organs in living patients.

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