A CLINICAL STUDY OF DIABETIC RETINAL ANGIOPATHY

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THE purpose of this paper is a limited clinical study of the type of diabetic patient who develops a retinal angiopathy, and of the possible mechanism of this development. It is limited by methods of examination—clinical only, by the instruments employed, by the number of patients investigated, by omission of many possible tests, such as fields of vision, acuity of vision, scotomata, etc., but it is believed that some light will be thrown on this puzzling problem and it is hoped that the attention of some investigators more happily situated than the writer will be drawn to newly elicited facts. From the very extensive literature in existence only a few quotations will be given.

The second question that will be examined is the well-known fact that the prognosis as regards life is not bad, but for vision, very gloomy. The retina may be almost completely destroyed, but the patient may be mentally alert.

Methods

Systolic Pressure (MX of the French writers).—The measurement was done on the wrist by palpation with the original Pachon's cuff (not that of Gallaverdin). The distension of the arteries due to the passage of the pulse wave is never seen in the retina, and the arteries there never collapse. This is due to the buffer action to the intra-ocular tension plus the peculiarity of the venous outflow of the retina. But this distension is clearly demonstrated in the limbs by the oscillometric method of Pachon.

For the purpose of this paper I selected the following groups of cases: five normal persons as controls, five with mild essential hyperpiesis (diastolic pressure 90-100), five with advanced essential hyperpiesis (diastolic pressure 100-150), and forty diabetics, of which fourteen had a retinopathy.

It seems, from the Table (p. 312), that the highest systolic blood pressure (average) was in the third group, where no retinopathy of any kind was seen. However, in the diabetic group the average systolic pressure for both wrists was $170\frac{1}{2}$, and the retinopathic group, actually lower, $163\frac{1}{2}$. This seems to justify the emphatic remark of Koyanagi (1935) "il faut donc abandonner l'axiome :—

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pas de rétinite diabétique sans hypertension." Folk and Sosskin share the same opinion, although the problem in my view is much more complicated.

Mean Blood Pressure (press. efficace).—This is an item of more importance than any other. While the systolic (MX) and diastolic (Mn) are correspondingly the highest and lowest level of pressure inside the arteries—the mean is the constant one that continuously forces the blood from the arteries into arterioles, capillaries, and veins. It can be measured *only* by using an oscillometer, and so building up an oscillometer curve.

The figures obtained vary with each individual patient, and in each limb of that patient. The mean pressure may form a high point or a plateau; in the latter case the line passing through the

middle point will be the mean pressure. The following charts will illustrate it, the ordinates being the units of oscillometry and the abscissae the corresponding readings of blood pressure in mm. of mercury (oscillometer of Boullite—Paris).

The mean pressure corresponds, as is seen in Charts 2 and 3, to the range of maximum oscillation. The height of this mean pressure, *ceteris paribus*, is the best indication of the state of the peripheral vascular resistance due to tonic (not spasmodic) contraction of the muscular media. Many authorities think that it is simply half of the pulse pressure (Best and Taylor, 1939; Macleod, 1938; Norris and others, 1927). It is nothing of the kind. Moreover, it may fluctuate independently (or nearly so) from both systolic and diastolic pressures. In one of my diabetics, a male aged 70 years, the reading was 160/90, mean 110, on May 31, 1948; on August 16, 1948, it was 180/80, mean 155; fundi were the same on both dates—meaning that the peripheral vascular resistance was on the increase.

Bailliant's method, in my opinion, is as necessary to a complete clinical picture as the measurement of the three blood pressures on the brachial or radial artery, and is as reliable. In this investigation one sees at first a faint tremor of the central artery on the disk, followed by pulsation—in the words of Duke-Elder; "the blood column flushes across the disk" (1940). It is obvious that the beginning of this pulsation is the measure of the mean pressure, not of the diastolic—which is evidenced by the tremor—because the mean pressure must be overcome before the artery collapses. Fritz (1946) thinks that the difference of the two applied pressures is the measurement of the rigidity of the muscular wall of the central artery. It is only partially so, because the difference between the diastolic and mean blood pressure is probably due to many factors, not well known at present. But whatever pressure will be applied on the eye-ball, it will never collapse the arteries on the retina even in the neighbourhood of the disk. This is why I cannot entirely agree with the opinion of Fritz that the cessation of the venous pulsation means the collapse of the retinal capillary tension—it is only partially true on retinal venous pulsation; see Pines (1948). The Table compares the mean blood pressure in the five groups.

Certain observations are rather interesting at this point. The 10 mm. difference in mean-pressure in normal persons is probably due to the action of the vasomotor system. No difference was observed in both groups of hyperpietics. In diabetics the difference is approximately equal (5 and 2½) in both females and males, but is rather large in the average taken of retinopathic results, eleven in males and even fifteen in the females. This result points to disturbance of elasticity.

Diastolic Pressure.—There is no general agreement on what is the level of diastolic pressure. The best summary is contained in the joint report of the Cardiac Society of Great Britain and of the American Heart Association (1939). While the British society considers the change from a clear to a muffled sound as the level of the diastolic pressure, the American committee recommends that if there is a difference between this point (change to the dull sound) and the level at which sounds disappear completely, the latter reading should also be regarded as a measure of diastolic pressure (*e.g.*, 80-70). I therefore relied only on oscillometry. Diastolic pressure is easily measured by the first larger oscillation, followed by a still larger one, thus forming a definite steep ladder in the curve if the measurement starts from zero, and *vice versa* if it starts from the systolic reading.

MacWilliam and Melvin (1914) say that “the Pachon and Diastolic index represented by the level of the armlet pressure immediately after declension, corresponded with remarkable exactness with the weakening and dulling of the sound, which constitutes the auditory index; the oscillation of the needle and the alteration of the sound varied together very strongly.”

It was the difference in the mean pressures that was noticed in the diabetics, especially in those with retinopathy; the same applies to the diastolic readings.

Oscillometer Index.—This is one of the best clinical methods of measuring the extensibility (*i.e.*, partly the elasticity) of the arteries of both wrists and ankles. In a normal young person the lower extremities have a larger, or at least equal, index to that of the wrists. It is different with advancing age. See Pines (1946) on physiological angiospasm of the retinal arteries. I had the opportunity of examining a man aged 44 years, with advanced nephritic retinopathy; the following were his readings:

$$\begin{array}{cc} \text{R.W.*} \frac{220(210)}{150-2} \text{ m/170} & \text{L.W.*} \frac{210(200)}{150-2} \text{ m/170} \\ \text{Oscill. index, R.A.* 7, L.A.* 3.} \end{array}$$

Up to 25 per cent. the difference of the oscillometric index may still be reckoned as a physiological one; higher than that—in my opinion—it is pathological. While, therefore, a certain amount of angiospasm of the lower extremities is seen in advanced hyperpietics, it is more accentuated in diabetics and extremely so in retinopathics. In fourteen cases of retinopathy, I saw it in twelve; on the other hand, I had fifteen diabetics with angiospasm, and in twelve I saw also the retinopathy—86 per cent. in the former

*R.W. = Right Wrist
*R.A. = Right Ankle

*L.W. = Left Wrist
*L.A. = Left Ankle

and 80 per cent. in the latter. Age makes no essential difference. (See Table, p. 309.)

Case Histories

Mrs. Z. I., aged 79 years

$$\begin{array}{cc} \text{R.W. } \frac{200(190)}{90-7} \text{ m/110} & \text{L.W. } \frac{190(180)}{90-4} \text{ m/100(110?)} \end{array}$$

R.A. $3\frac{1}{2}$, L.A. $4\frac{1}{2}$; fasting blood sugar 140. Diabetic for 8 years, taking 14 units of insulin daily; advanced sclerosis of the retinal vessels, no retinopathy.

Mrs. D., aged 65 years, on the other hand

$$\begin{array}{cc} \text{R.W. } \frac{220(210)}{70-4} \text{ m/90} & \text{L.W. } \frac{180(170)}{70-4} \text{ m/90} \end{array}$$

B.A.* nil; fasting blood sugar 182. Diabetic for 14 years, taking 38 units of insulin daily. Both fundi—advanced sclerosis of the retinal vessels. No retinopathy. Examined again in two months' time, she gave the reading:—

$$\begin{array}{cc} \text{R.W. } \frac{160}{80-5} \text{ m/115; B.A.—1; both eyes—idem.} \end{array}$$

Mrs. S., aged 56 years, diabetic for 10 years; fasting blood sugar 220; taking 60 units of insulin daily

$$\begin{array}{cc} \text{R.W. } \frac{220(210)}{120-6} \text{ m/140} & \text{L.W. } \frac{200(190)}{100-2} \text{ m/120} \end{array}$$

B.A. $\frac{1}{2}$; R.E.* retinopathy with haemorrhages and exudation.

This is a peculiar form of angiospasm, occasionally accompanied by intermittent claudication of which this patient complained.

A man aged 59 years, on the other hand

$$\begin{array}{cc} \text{R.W. } \frac{230}{90-4} \text{ m/110} & \text{L.W. } \frac{230}{90-5} \text{ m/110} \end{array}$$

B.A. nil; fasting blood sugar 133, diabetic $4\frac{1}{2}$ years, taking 6 units of insulin daily, was quite happy.

A man aged 44 years, however,

$$\begin{array}{cc} \text{R.W. } \frac{140}{90-3} \text{ m/120} & \text{L.W. } \frac{140}{90-3\frac{1}{2}} \text{ m/120} \end{array}$$

R.A. $2\frac{1}{2}$; L.A. 5; diabetic 2 years, taking 24 units of insulin daily; (fasting blood sugar not known); R.E. retinopathy with considerable amount of exudation and a few small aneurysms, had intermittent claudication in his right leg. One must take into consideration that his mean pressure was rather high as well, and that the combination of both factors probably produced the claudication.

It is important to note that in my series of cases, a few were suffering from old gangrene of the toes of both feet.

Such was *H. S., a man aged 70 years*, diabetic for 12 years, taking 37 units of insulin daily. His readings were

$$\begin{array}{cc} \text{R.W. } \frac{160}{90-5} \text{ m/100} & \text{L.W. } \frac{150}{85-6} \text{ m/105} \end{array}$$

R.A. 2; L.A. $\frac{1}{2}$; lentic opacities. No retinopathy. Three months afterwards his readings were

$$\begin{array}{cc} \text{R.W. } \frac{180}{80-4\frac{1}{2}} \text{ m/155} & \text{L.W. } \frac{180}{80-4\frac{1}{2}} \text{ m/140} \end{array}$$

R.A. 2; L.A. 1; urine sp. qs. 1,025; sugar plus; albumin—fasting blood sugar 200 mg.

*B.A. = Both Ankles

*R.E. = Right Eye

A woman, aged 59 years, diabetic 20 years, taking 20 units of insulin daily, gallop rhythm of heart due to splitting of the second sound, had an initial gangrene of both big toes. Her readings were

$$\begin{array}{cc} \text{R.W. } \frac{170}{90-3\frac{1}{2}} \text{ m/110} & \text{L.W. } \frac{160}{90-4} \text{ m/110} \end{array}$$

R.A. 4; L.A. 4. Diabetic retinopathy of both eyes, but no haemorrhages.

In my opinion, the gangrene in these cases was due to disturbance of the capillary, not of the arterial, circulation. The angiospasm then is really an arterial reaction of local or general aetiology, quite separate from the height of blood pressure, but more frequently seen in combination with hypertension, probably because the arteries then are more easily excited and react more violently. Plesch (1937) also points out that normally the arteries are distended about 100,000 times in 24 hours and, provided these are not distended too much, their elasticity does not suffer. X ray of the lower limbs, performed in a few cases of advanced angiospasm, showed diffuse calcification of the arteries of the calf. As the reader may observe above, the process may be reversible. The contrary may also occur.

An old man, a non-diabetic and a heavy smoker, with a past history of pulmonary tuberculosis, had, when seen at his home, the oscillometer index of both ankles, 1 or $1\frac{1}{2}$. Admitted to the London Jewish Hospital and put to bed, he had an index of $\frac{1}{2}$ in the left ankle, with blood pressure of 140 and 1 with 120. But in the right ankle, he had $\frac{1}{2}$ with 120 and nil with 140.

While the upper limbs are usually immune, no completely satisfactory explanation is available as to why the lower limbs should be chiefly affected, but it is a well-known clinical fact. There are many factors causing it—the upright walking position, longest distance from the heart, difficulties of venous outflow, etc.

Here, in conclusion, is a case of extreme hypertension combined with a mild diabetes.

Mrs. E. T., aged 57 years, had had 12 children. She was slightly cyanotic, easily dyspnoetic on very mild exertion, and had been a diabetic for $1\frac{1}{2}$ years. Fasting blood sugar was 125 on June 5, 1947, and 100 on February 10, 1948. She was taking 33 units of insulin daily.

$$\begin{array}{cc} \text{R.W. } \frac{280}{130-3\frac{1}{2}} \text{ m/180} & \text{L.W. } \frac{270}{130-3} \text{ m/200} \end{array}$$

B.A. 1. Fundi showed severe degeneration of the arteries, which were thin, tortuous, nearly silver wire. Hour-glass compression of the veins by the arteries, no haemorrhages or exudation seen.

It is obvious from the Table that the age of the retinopath is actually lower than that of the average diabetic, and that the retinopaths have a longer history of disease than the diabetics.

TABLE
Particulars of Groups Discussed

Group	Normal Persons (5)	Hyperpiesis		Diabetes (40)					
		Mild (5)	Advanced (5)	Without retinopathy (26)			With retinopathy (14)		
				Average	Males	Females	Average	Males	Females
Average Age ...	26	52	56	61	59	62	57	50	58
Duration of Disease (years)	—	—	—	10	5	12	13	6	14
Fasting Blood Sugar	—	—	—	189	176 $\frac{5}{9}$	194	198 $\frac{1}{4}$	225	186
Insulin (units)	—	—	—	29	25	30	32 $\frac{3}{2}$	25	30
Blood pressure									
Systolic R.W.	122	176	200	175	149	186	154	180	149
L.W.	122	164	196	166	137	177	173	170	175
Mean R.W.	100	116	134	106 $\frac{1}{2}$	100	111 $\frac{1}{2}$	120	115	121
L.W.	110	116	134	101 $\frac{1}{2}$	97 $\frac{1}{2}$	106 $\frac{1}{2}$	109	120	106 $\frac{3}{5}$
Diastolic R.W.	88	100	120	91	84	94	98 $\frac{3}{4}$	105	97 $\frac{6}{3}$
L.W.	88	100	120	87	73	92	94 $\frac{0}{14}$	85	91 $\frac{7}{12}$
Oscillometer									
R.W.	2 $\frac{0}{10}$	4 $\frac{3}{4}$	3 $\frac{5}{8}$	3 $\frac{1}{2}$	4 $\frac{1}{2}$	3 $\frac{27}{8}$	3 $\frac{8}{14}$	4 $\frac{1}{2}$	3 $\frac{5}{12}$
L.W.	3	4 $\frac{3}{8}$	4 $\frac{1}{10}$	3 $\frac{2}{8}$	4 $\frac{4}{10}$	3 $\frac{2}{8}$	3 $\frac{5}{8}$	3 $\frac{1}{2}$	3 $\frac{1}{12}$
R.A.	4 $\frac{1}{2}$	4 $\frac{7}{10}$	3 $\frac{2}{5}$	2 $\frac{1}{2}$	4 $\frac{3}{11}$	2 $\frac{5}{8}$	1 $\frac{2}{3}$	1 $\frac{1}{4}$	2 $\frac{1}{12}$
L.A.	4 $\frac{1}{2}$	4 $\frac{7}{10}$	2 $\frac{3}{5}$	2 $\frac{7}{8}$	4 $\frac{4}{11}$	2 $\frac{13}{8}$	1 $\frac{2}{8}$	2 $\frac{1}{4}$	1 $\frac{5}{13}$

R.W. Right Wrist.
R.A. Right Ankle.

L.W. Left Wrist.
L.A. Left Ankle.

Discussion

In estimating the oscillometer index, we have to compare that of the lower extremities with that of the wrists, but especially the difference between both ankles.

The diabetic who develops a retinopathy is a definite type where the most prominent sign is angiospasm of both lower extremities. The opinion of Ballantyne and Michaelson (1948) is different—"in diabetes there is no discovered correlation between the fundal picture and the age of the patient, the blood pressure, or the severity of the disease." As quoted in the *Traité d'Ophthalmologie*, some authorities had 58 retinopaths in 398 diabetics. Grafe (1923)

saw 80 in 500; Folk and Soskin (1935) had 33 per cent.; and Taubenhause (1935) some haemorrhages in 40 per cent., but in 80 per cent. when they were hyperpietics. Redslob (1948) saw retinopathy in 31 diabetics of 52 to 78 years of age, and none in 51; Hanum (1938) saw retinopathy in 195 cases out of 966. Duration of diabetes is 5 years for retinopathy according to Krause (1930) and 10 years according to Braun (1935, etc.). Redslob estimates glycosuria as 150-250 mg. Elwyn (1945) quotes 45 diabetics of an average age of 55 years (24 to 73; 33 females, 12 males); there was mild nephritis in eight, arterial hypertension in fifteen, arterio-sclerosis in thirteen, lenticular opacities in eleven, and retinopathy in 25; the average systolic pressure was 154 (96-270), the diastolic 85 (60-130), and fasting blood sugar 84-289 (average 141). According to Ballantyne and Michaelson, in a large series of diabetic patients with retinal changes, over 50 per cent. had no abnormality of blood pressure. Other writers quoted by Redslob and the *Traité d'Ophthalmologie* found evidence of general arterio-sclerosis (athero-sclerosis?) in 45 diabetics and retinopathy in 25, and Braun (1935, etc.) found the percentage of arterio-sclerosis equal between diabetics and non-diabetics of the same age. But Altnow (1927) found that this sclerosis starts with diabetics at 33 years and with non-diabetics at 57. Dry and Hines (1941) found retinopathy in 47 per cent. of the diabetics, but in 17 per cent. of the retinopaths there were no signs of arterio-sclerosis. Hanssen (1929), Doggart (1930), Foster-Moore (1915), and Gradle (1926) are of the opinion that retinopathy is of arterio-sclerotic origin. Shephardson and Crawford (1931) deny the connection of retinopathy with diabetes and ascribe it only to arterio-sclerosis. Franceschetti and Streiff (1939) found hypertension in 87 per cent. of 13 retinopaths, and two-thirds of them had a very high diastolic pressure. Vom Hofe saw 45 cases of retinopathy, 32 of them with hypertension; Hanum (1938) found 75 per cent. of hypertension in 35 cases of retinopathy. Onfray (1918, etc.) saw three patients with normal blood pressure in 24 retinopaths. Mylius (1936) does not think that hypertension has any connection with retinopathy. Crocco (1932), Cammidge (1930), and Braun (1935, etc.) found only 43 hypertension cases in 111 cases of retinopathy. Weill (1938) found the systolic pressure over 150 in 72 per cent. of retinopaths; but 37 per cent. of his diabetics had no retinopathy. In the opinion of Kaufmann and Cosla (1940), over 50 per cent. had no abnormality of blood pressure. Schmid (1939) thinks that hypertension helps to develop a retinopathy. Volhard (1931), Arruga (1932), and others think that retinopathy develops only with hypertension. More than 85 per cent. of the retinopaths in *Traité d'Ophthalmologie* were hypertensive and in 30 per cent. the kidney function was damaged. Yet in

my series of forty diabetics, fourteen had a retinopathy (35 per cent.), 28 being females and twelve males (females 70 per cent., males 30 per cent.). Among the females were twelve retinopathies (30½ per cent.) but only 5 per cent. out of all the forty diabetics were males; the average age was nearly four years lower than in average diabetics (61-57); 9 in males, and 3½ in females. The mean blood pressure and the diastolic pressure were definitely higher in the retinopathies. The systolic pressure is of little importance; it is not connected with the rise of the diastolic and the mean pressure. *The retinopathy in my cases is definitely connected with mild hypertension and advanced angiospasm of the lower extremities.*

The kidney function was not damaged, as measured by blood urea in some cases (Pines, 1931). I still maintain that the real test of a special form of kidney damage is oedema of the retina. On the other hand, nephrosclerosis will be present in all cases of general sclerosis, but nephritic retinitis was not seen in any of my cases, even with the highest blood pressure (280/130).

The Possible Mechanism of Diabetic Retinal Angiopathy

Pathology.—Wolff (1944) states that the earliest change is the presence of fatty droplets in the endothelial cells of the retinal veins and capillaries; phlebosclerosis of the larger veins with later hyalination of the walls; some noxious chemical agent in the blood stream and almost specific to certain cases of diabetes is responsible for the changes in the vessels, particularly the veins, venules, and capillaries. Ballantyne and Michaelson (1948) found that the changes begin with fatty infiltration and swelling of the endothelium of the smaller vessels and proceed to capillary and venous stasis. Elwyn (1945) feels that the small retinal haemorrhages observed in diabetes have no relation to the vascular changes of aging, sclerosis, hypertension and obstruction of the veins, but are rather dependent on pre-static condition of the capillaries of the retina, which is in some way related to moderate hyperglycaemia. Redslob (1948) thinks "that the haemorrhages are produced by diapedesis, that the veins and capillaries are showing sclerotic changes in their walls with hyaline degeneration." The white spots are formed by fibrin round the vessels but does not represent necrotic foci, but he quotes the opinion of Beauvieux and Pesme (1923) that the haemorrhages are due to hyperglycaemia, and the white spots to impairment of the kidneys. L. Russo (1925), Lawrence (1936), and Staupendahl (1926) saw endarteritis obliterans of the small vessels. Bonnet and Bonamour (1938) think that the veins are chiefly attacked; the same is the opinion of Dry and Hines (1941).

According to *Traité d'Ophthalmologie* the changes in the diabetic

arteries are chiefly a preponderance of cholesterine and calcium. Hyperglycaemia injures the endothelium, cholesterine impregnates it, and calcium helps to obliterate the arterioles. The veins are attacked not only in the retina, but in the choroid as well. The haemorrhages are situated in all layers of the retina, including that of the pigment epithelium, and rods and cones. The exudate is fibrinous.

The Ophthalmoscopic Picture.—This is chiefly represented by white spots of exudation, minute venous aneurysms, as first explained by Ballantyne, and various forms of retinal haemorrhages. Sclerosis of the arteries is present (as opposed to that of the veins) only when the blood pressure is raised. But I would like to draw attention to a peculiar shining reflex, slightly similar to the water-silk reflex of the young, that is seen in some peculiar forms of advanced hyperpiesis—due, in my opinion, to sclerotic changes in the capillary bed, and not connected in cases of diabetic angiopathy with the degenerative changes in the arteries, as in the following case.

A man, aged 44 years, diabetic for two years, blood sugar unfortunately not established, had the following readings

	140		140
R.W.	— m/120	L.W.	— m/120
	90.3		90.3½

R.A. 2; L.A. 5, with intermittent claudication in the right calf; R.E. a considerable amount of exudation near the macula and a small aneurysm at or near a small independent vein. L.E. starting degeneration of the macula and a small aneurysm at 3 o'clock. B.E. peculiar reflex from the retina of both eyes.

The exudation, as is well known, is waxy in appearance, sharply limited and hardly changeable. In hypertension the exudation is usually not far from a large vein or artery, more bluish in appearance, and has more rugged borders; after a week or two in the majority you see newly formed capillaries encroaching from the periphery. I have seen nothing of this kind in diabetic angiopathy. Sometimes, in about two cases out of fourteen, there was exudation, but no haemorrhage; in the rest they were combined with aneurysms, as pointed out by Ballantyne. Undoubtedly he and Loewenstein are right in saying that this is, at present, the earliest manifestation of retinopathy. I applied the dynamometer of Baillart in many cases—without measuring the intra-ocular tension—but did not find any peculiar difference in cases of arterial hypertension. I cannot agree with the opinion of Espildora-Lugue (Sorsby, 1948) that there is no brachial hypertension without increase of the retinal pressure. These cases are fortunately rare. The patient is very giddy, and liable to have coronary thrombosis. Here is the record of one illustrative case.

Mrs. B., aged 60 years, with essential hyperpiesis for years; advanced retinal sclerosis. From time to time—foci of retinomalacia. Very giddy.

R.W.	$\frac{230(220)}{120-3}$	L.W. <i>idem</i> , B.A. 3.	Intra-ocular tension 15.
In sitting position		Bail. R.E. 25, <i>i.e.</i> , Mean 20.	
		L.E. 25, <i>i.e.</i> , Mean 20.	
In recumbent position		Bail. R.E. 40(35).	
		L.E. 45(40).	

Died within a year from two attacks of coronary thrombosis.

For this reason Bailliart's reliable method did not show any special results in diabetic angiopathy, which is due to a capillary degeneration, not to an arterial one.

Venous Pressure.—The primordial difficulty of measuring venous pressure is in the retina, and its intricate connection with the intra-ocular tension. That is why anybody who tries to do it is really measuring the intra-ocular tension or the tension in the ophthalmic vein—the latter being already part of the brain system.

Until a method is found to dissociate the venous pressure and the intra-ocular tension from each other, the result for both is nearly equal. That is why I cannot agree with the opinion of Fritz (1946) and others.

The general venous pressure as examined by a large bore needle, introduced in the cubital vein of the patient and connected with a special manometer, was found within normal limits—14-16 cm. of water for the female, and up to 16-18 cm. for the male. Again the result is not surprising, as a raised venous pressure is the earliest sign of impending heart failure and has nothing to do with diabetes.

Capillary Circulation.—In my opinion, the vascular tree, anatomically, may be the same everywhere in the body, but physiologically and pathologically it is nothing of the kind. This chief difficulty in clinical examination is greatly increased when we come to speak of the capillary bed, and especially that of the retina. Plesch is right when he expects a very intimate connection between the local capillaries and products of cellular metabolism ("metabolites"). The capillaries of the lungs are specially adapted for oxygen metabolism, those of the liver for glycogen, etc. Even about the capacity of the capillary bed, opinions are widely divergent (See Plesch, 1937, as against Krogh). The capillaries of the soles of the feet are probably adapted to withstand an enormous outside pressure—otherwise necrosis of the soles would occur in the standing position. The capillaries of the skin can withstand, according to Wright (1945) a pressure of 100 mm. of mercury—an incredible pressure for retinal capillaries.

Thus, at least as far as the retina is concerned, we have no methods at all of measuring their vital capacities directly. But one fact emerges strongly: in the lower extremities of retinopaths we have to deal with angiospasm of the arteries and arterioles, but not of the capillaries. More than that (in two cases, where the patient had an incipient or a definite gangrene of the big toe and of the soft parts of the toes, there was no angiospasm of the arteries at all, and in the majority of the cases of extreme or advanced angiospasm there was no gangrene of the toes) the two conditions may be, and often are, quite separate. Moreover, as mentioned previously, in diabetic retinal angiopathy the ophthalmoscopically visible arteries are not much changed, unless the blood pressure is raised but the exudation and minute venous aneurysms are already present and situated usually below the nerve fibre layer, or the patient is advanced in age (senile changes).

I would say that the extent of exudation and haemorrhages in diabetes is connected with little degeneration—of primary and secondary arterial branches—just the opposite to what is usually seen in arterial hypertension, where the exudation and haemorrhages usually appear after the degeneration of the arteries is very advanced indeed.

According to the *Traité d'Ophthalmologie*, Safar (1935) thinks that the lesions are chiefly those of small blood vessels, invisible by the ophthalmoscope. In short, contrary to those of the lower extremities, the capillaries of the retina are involved and the arteries are not. How can one explain it? I think it is axiomatic that the tissues fated to do harder work are naturally constructed to withstand the strain. A baby is born with the skin of his soles thicker than that of the rest of the body; the structure of the aorta is different from that of the medium arteries, etc. All the arteries and capillaries in the body are built to withstand a considerable pressure from inside, because on the outside the pressure is not higher than that of the venous pressure—18 cm. of water. The pressure inside the brain, as expressed in the figures of cerebrospinal liquid pressure, is also very low. "A high venous pressure gradient would necessitate a high capillary pressure and give rise to excessive pulsation in the veins, which would seriously damage the elastic properties of the walls of those vessels" (Plesch, 1937). And this is so with the retina, even in normal cases. The blood vessels of the eye, including those of the retina, are caught between the non-elastic sclera and non-elastic gel of the vitreous body and are constantly subjected to an *outside* pressure of 15-18 mm. of mercury, right from the late period of the intra-uterine life. Supported continuously by a very considerable pressure from outside, they have no need to develop powerful vascular walls and

therefore are more easily affected than those in other parts of the body. On the other hand, this may explain the fact that the cerebral vessels of a hyperpietic, not supported from outside, rupture much more frequently than the retinal ones—a striking contrast with diabetics. The vascular system of the kidney with its capsule more elastic than that of the sclera, but less than that of the spleen or liver, may be in a similar position; taking that and the very similar structure of the nephron and the retina in its relation to the vascular system (see Pines, 1931, on renal nephritis) into consideration, one wonders if this is not a possible clue to the striking parallelism of the pathology of the retina (not choroidea) and of the kidney. And the newest form of nephritis, described as due to sclerosis of the smaller vessels between the glomeruli, may it not be explained by angiospasm of those vessels? Already Leber (1916) has stated that “the retinal changes in true or albuminuric retinitis can recede if the basic pathological process in the kidney is healed or improved. In good cases even highly advanced retinal changes can recede completely”.

After the experiments of Trueta and his co-workers this remarkable capacity of the kidney is easily explained by the angiospasm of its vascular tree.

I repeat the same opinion now (but with, I believe, an anatomical basis): hyperpietic retinopathy is due to sclerosis of the larger arteries and arterioles; renal retinitis is due to the attack of the toxin on all branches of the vascular tree and their spasm; diabetic retinopathy attacks chiefly the capillary bed and the venous system.

Angiospasm is chiefly the attribute of renal and diabetic retinopathy and of toxæmia of pregnancy.

Whatever it is, I think that the intra-ocular tension makes the walls of the retinal arterial system more fragile, and the capillaries are, of course, the weakest link in the chain. The veins again suffer because they must have an intravenous pressure much higher than usual, as the outflow of blood must be able to overcome the intra-ocular tension. There is then a vicious circle—a system with weak muscular walls must be able to develop a fairly high intravascular tension. Two additional factors come into play. One is the fact that with the vascular spasm of the lower extremities the inflow of blood to the upper part of the body is increased. The oscillometer readings of both wrists in the Table well demonstrate this. The other is even more important: the exudation in retinopathy is fibrinous; there is no necrosis, and it is stationary for months, if not longer. Admittedly I did not examine the visual fields of my diabetics for scotomata (a really necessary additional factor), but the absence of retinal necrosis means only

one thing, that the circulation is still going; and it means that the capillaries, degenerated, are closing and opening up again, a form of angiospasm. If this be so, what will happen to the venules? Their walls are weakened by the unknown toxic factor and subjected to a sudden increase in the inflow of blood, not sufficient to burst them, but sufficient to form an aneurysm. I described and illustrated in sclerosis of the retinal vessels (Pines, 1929) a similar venous aneurysm in even a strong vein, which being crushed by an artery, formed this aneurysm on the proximal side of the crossing, where the blood stream, after passing under an artery, strikes and dilates a weakened venous wall. To that must be added the generous venous stasis due to the diminished *vis a tergo* of capillary pressure, conditioned by the degeneration of the capillary walls and added angiospasm. Then the peculiar and rare tortuosities of the veins, as described and illustrated by Ballantyne and also by Lowenstein, may be due not only to the degeneration of their walls but also to the diminished *vis a tergo* and to the undiminished intra-ocular tension at their exit from the retina at the disk. It would stimulate the well-known phenomenon of a briskly flowing stream of water, less tortuous than the sluggish one. The tremendous haemorrhages of the final stage are due to the rupture of the large veins, and not to diapedesis.

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