THE SIGNIFICANCE OF CONJUNCTIVAL ANEURYSMS IN DIABETICS*

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VASCULAR disease in diabetes remains a major problem yet to be solved. Retinal haemorrhages and retinal exudates have been considered diagnostic signs of diabetes and, although many have clung to the belief that these are arteriosclerotic or renal in nature, proof that they are diabetic in origin is accumulating.

Ballantyne (1943) demonstrated that some of the small spots of blood seen in the retina, which previously were considered haemorrhages, were actually aneurysms. He described them as being small, spherical forms attached to the finer perimacular venules like berries to twigs. He also demonstrated changes in the retinal veins, consisting of general and localized expansions, beading, loops, kinks, diverticula, fine new vessels on the surface of the retina, and new vessels projecting into the vitreous. He further noted fatty degeneration in the vessel walls, including the capillaries, and felt that ectasiae leading to aneurysms developed where the fatty changes were most marked.

Friedenwald (1948) added to our knowledge of these aneurysms by showing that the sacs were often incompletely lined with endothelium. He therefore assumed that the leakage of blood occurred first, and that the endothelium grew from the vessel to encapsule the blood. He stated that the process develops from a break in a capillary wall leading to a persistent slow leak of corpuscles; the hole shows little tendency to heal, but instead endothelial cells grow out to surround the extravasated blood cells. On the basis of this hypothesis, he suggested that hard white exudates could be explained as the consequence of still smaller breaks in the capillary walls through which plasma, but not red cells, escapes.

Ashton (1949) reported the post-mortem findings of 21 diabetics. The eyes, including the retina, iris, ciliary body, choroid, and conjunctiva, were examined for evidence of vascular changes. True aneurysms were found in the retina. One type of aneurysm showed an afferent and an efferent vessel; the basement membrane of the vessels extended into the wall of the aneurysm. Another type arose from one side of the vessel while the opposite side remained normal. No aneurysms were found in the iris, ciliary

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body, choroid, or conjunctiva, nor in the cerebral vessels, meninges, omentum, peritoneum, pleura, pericardium, bladder wall, liver, or kidney capsule.

Ashton noted the hyaline masses in the glomeruli in inter-capillary glomerulosclerosis, and felt that these masses and the retinal aneurysms were manifestations of the same pathological process modified by different anatomical structures. Although he did not find aneurysms in other parts of the body, he suggested that the hyaline masses in the glomerular tufts in inter-capillary glomerulosclerosis were occluded aneurysms.

The possibility of aneurysms being present in parts of the body other than the retina and glomeruli still remains despite their absence in Ashton's 21 autopsies. Aneurysms are difficult to see in sections. Only if the cut happens to pass in a certain plane does the distinction between vessel and aneurysm become apparent. In any given block of tissue the number of aneurysms may not be great, and many sections would need to be cut, and to be examined with the greatest care, before one aneurysm was found. Some other method, whereby larger areas of tissue can be quickly surveyed, is necessary before we can come to a decision concerning the presence of aneurysms in any particular tissue. The conjunctiva presents an opportunity for a relatively quick survey of a large area, and for accurate examination of detail. More than a year ago we noticed conjunctival aneurysms in diabetics, using the high power of the slit-lamp. We have endeavoured to determine the relationship of these aneurysms to diabetes. Other places in the body, such as the nailbed, may present opportunities for the study of aneurysms. We have, however, restricted our efforts to the conjunctiva.

FIG. 1.—Conjunctival aneurysms in a diabetic.

FIG. 2.—Conjunctival aneurysms in a diabetic.

Method

We studied approximately one hundred diabetics seen at the Toronto Western Hospital Diabetic Clinic, and on admission as in-patients. For controls we examined fifty patients who came to the eye clinic for routine refractions with no history of diabetes, or as in-patients with fractures, herniae, acute appendices, etc. We chose the controls from an age group to coincide with that of the diabetics. We charted the patients' age, sex, the duration of their diabetes, blood pressure, blood non-protein nitrogen, blood cholesterol, urine analysis for blood, albumin, and capillary fragility. The capillary fragility was estimated by placing a blood-pressure cuff just above the elbow, keeping it distended to 80 mm. Hg for five minutes, and counting the number of petechiae per square inch on the anterior surface of the forearm. The patients' eyes were examined, including the vision, conjunctiva, iris, lens, and fundus.

FIG. 3.—Conjunctival aneurysms in a diabetic.

FIG. 4.—Conjunctival aneurysms in a diabetic.

Results

Conjunctival aneurysms were found in 55 per cent. of the diabetic and in 14 per cent. of the non-diabetic patients. The appearance of the aneurysms (Figs 1-4) is interesting. Two types can be identified. The first type is a true berry aneurysm, as described and seen by Ballantyne and others in the fundus, to which a vessel can, or cannot, be traced. These aneurysms are purplish in colour, as distinct from small haemorrhages which are bright red. The aneurysms have sharp borders, and round, smooth surfaces. They may be seen anywhere in the conjunctiva,

TABLE I

Groups		Diabetics				Normals	
		With Retinopathy (1)		Without Retinopathy (2)		(3)	
		Conjunctival Aneurysms	No Conj. Aneurysms	Conj. Aneurysms	No Conj. Aneurysms	Conj. Aneurysms	No Conj. Aneurysms
Average Age (years)		62	55	53	60	70	60
Average Duration (years)		13	13	5.5	6.1		
Average Blood Pressure (mm.Hg)	Systolic	168	151	130	154	139	140
	Diastolic	78	82	73	80	78	78
Albuminuria	+	1	3	0	1	0	3
	-	38	20	22	24	6	46
Benzidine	+	3	1	2	2	0	5
	-	33	19	16	24	6	46
Average Blood Cholesterol (mm. %)		196	239	201	223	160	176
Average Blood N.P.N. (mm. %)		42	46	40	40	45	47
Average Capillary Fragility (petechiae)		34	52	39	18	18	5

at the limbus or towards the fornix, and are either deep or superficial in the conjunctival stroma. They do not absorb but can be seen unchanged as to size, shape, and position after several months. This type we regard as the one which may be related to diabetes. The second type appears as an aneurysmal dilatation of the veins. It also can be seen anywhere in the conjunctiva, but is commonly found near an area of inflammation, as adjoining a pinguecula, and in old people presumably accompanying severe arterio-sclerosis. These dilatations are common, and, as we were doubtful of their significance, we did not include them in our records of aneurysms.

Other changes were noted which may or may not be associated with the aneurysms. Areas of haemorrhages into the subconjunctival tissue were seen. Some of the veins appeared dilated and tortuous, with sludging of the blood, and slowing of the flow. Aqueous veins were noted in many of the patients. Deposits of hyalin-like material were evident in the conjunctival stroma.

For the purposes of analysis we have allotted the patients to three groups of approximately fifty each, consisting of diabetics with retinopathy, diabetics without retinopathy, and normal individuals. The summary of the various findings is given in Tables I and II, and Fig. 5. All the findings can be considered negative, except that aneurysms were more frequently found in

TABLE II
Average Findings for Diabetics with and without Conjunctival Aneurysms.

Aneurysms	Sex	Age	Duration (years)	Blood Pressure		N.P.N.
				Systolic	Diastolic	
With	36 ♀ 19 ♂	55	9.1	139	78	41.2
Without	36 ♀ 8 ♂	57	9.3	152	78	46

Aneurysms	Chol.	Albuminuria	Benzidine	Cap. frag.	Lens	Fundi	V.A.
With	194	21— 31 trace 1+	43— 4+	39	25+ 29—	33+ 21—	20/56
Without	229	12— 26 trace 5+	38— 4+	16	12+ 27—	21+ 45—	20/42

FIG. 5.—Relationship between conjunctival aneurysms and retinopathy.

diabetics with retinopathy than in diabetics without retinopathy, and in diabetics without retinopathy than in controls (Fig. 5).

Discussion

In this study, conjunctival aneurysms of the berry type were found four times as commonly in diabetics as in normal people. They were found in 62 per cent. of diabetics with retinopathy, and in 48 per cent. of diabetics with no retinopathy. The results are negative in all respects as regards age, duration of diabetes, blood pressure, albuminuria and haematuria, blood cholesterol and non-protein nitrogen, and capillary fragility.

In a previous report (McCulloch and Pashby, 1948) we found a relationship between diabetic retinopathy and age, and between retinopathy and duration of diabetes; but not between retinopathy and many other laboratory and clinical findings (Table III). Therefore it is not surprising that the presence of conjunctival aneurysms is not related to these many findings.

The 14 per cent. occurrence in normals is interesting. Aneurysms certainly occur in normals, hence their presence in the conjunctiva is not diagnostic but rather suggestive of diabetes. They may indicate a widespread tendency among the general population toward diabetes. The known hereditary character of diabetes (Joslin and others, 1947) suggests that such may be the case. We

TABLE III

*Comparative Findings for Diabetics with and without Retinopathy.
(Study of 119 Diabetics, 1948)*

Retinopathy	Age (years)	Sex (%)		Duration (years)	Severity (%)			Control (%)	
		♀	♂		mild	mod.	severe	good	poor
With ...	64	56	44	13	28	47	25	50	50
Without ...	62.5	48	52	7	22	53	25	37	63

Retinopathy	Serum Proteins			Proth. time (sec.)	Chol. (mg.)	N.P.N. (mg.)	Albuminuria (%)		Blood Pressure	
	total	alb.	glob. (mg.)				+	○	systolic	diastolic
With ...	7.1	4.15	2.8	15	160	42	50	50	160	91
Without ...	7.4	4.6	2.6	15	160	33	19	81	155	84

have seen two cases of massive aneurysms in the conjunctiva which were presumably due to angiomatosis. The patients were both young adult males, one diabetic and one not diabetic.

The presence of aneurysms in the conjunctiva suggests that they occur in most tissues of the body. The fact that aneurysms are seen in the retina and that changes of a similar nature can be found in the kidney, but have not been described in other tissues, implies that the aneurysms are present to a different degree in different tissues. The form which they take may vary slightly from one tissue to another.

The circulation to the middle layers of the retina, to the glomeruli of the kidney, and to the islets of Langerhans of the pancreas is similar (Beck and Berg, 1931; Dewitt, 1906; Bensley, 1911). The only vessels present in each are capillaries, which might be considered as a carefully segregated end-bed, designed to subserve the rapid transfer of metabolic products or fluid. This fact leads us to search for a similar pathological picture in these three organs.

The hyaline change which has long been known to occur in the islets of Langerhans (Opie, 1901) is of particular interest. In standard sections the material may appear as a thickening of the reticulum, as small round balls, as larger masses, or as a complete replacement of the islet tissue by hyalin (Figs 6-9, overleaf). The

FIG. 6.—Islet of Langerhans from a case of diabetes. Taken at autopsy. Haematoxylin and eosin stain.

FIG. 7.—Islet of Langerhans from a case of diabetes. Taken at autopsy. Haematoxylin and eosin stain.

FIG. 8.—Islet of Langerhans from a case of diabetes. Taken at autopsy. Haematoxylin and eosin stain.

FIG. 9.—Islet of Langerhans from a case of diabetes. Taken at autopsy. Haematoxylin and eosin stain.

hyalin might come from degeneration of the islet cells or as overgrowth from the capillary walls. The latter possibility suggests that the hyaline changes in the pancreas, in the glomerular tufts, and in the retina, are comparable. All three changes may be considered as an increase in the intercellular ground substance. In the retina it appears as hyaline changes in the walls of microaneurysms, in the kidney it appears in the glomeruli as hyaline masses, and in the pancreas it appears in the islets in whorls and balls next to the vascular clefts. This increase in intercellular substance would decrease the blood supply of the islets, decrease the adsorption of substances from the blood, and decrease the transfer of insulin into the blood.

The hyaline changes may be the cause of diabetes. Our experience, and that of others (Waite and Beetham, 1935; Wagener and others, 1934) has shown that the retinal lesions are not directly related to the diabetes. Severe retinopathy may be seen in patients with mild diabetes of short duration, under good control. Similarly one may find no retinopathy in patients with severe diabetes of long duration, and under poor control. This lack of correlation finds explanation if we consider the hyaline changes in the pancreas as a cause of the diabetes. Then diabetes is seen as a general vascular disease of which the changes in the pancreas are only a part. If the vascular change is more advanced in the retina than it is in the pancreas, the retinopathy would outstrip the severity of the diabetes. On the other hand, if the vascular change is more advanced in the pancreas, severe diabetes would be possible with little or no retinal change. The development of intercapillary glomerulosclerosis in some patients, but not in others, can be similarly explained. Finally, the presence of conjunctival aneurysms demonstrates the widespread character of this disease.

Conclusion

Aneurysms can be found in the capillaries of the conjunctiva, and are related to the presence of diabetes, and to the incidence of diabetic retinopathy. Diabetes may be part of a generalized vascular disease which affects the retina, glomeruli, islets of Langerhans, and conjunctiva.

REFERENCES

- ASHTON, N. (1949). *British Journal of Ophthalmology*, **33**, 407.
 BALLANTYNE, A. J. and LOEWENSTEIN, A. (1943). *Trans. Ophthalm. Soc. U.K.*, **63**, 95.
 BECK, J. S. P. and BERG, B. N. (1931). *Amer. J. Path.*, **7**, 31.

- BENSLEY, R. R. (1911). *Amer. J. Anat.*, **12**, 297.
- DEWITT, L. M. (1906). *J. exp. Med.*, **8**, 193.
- FRIEDENWALD, J. S. (1948). *Trans. Amer. Acad. Ophthalm. Oto-laryng.*, **53**, 73.
- JOSLIN, E. P., ROOT, H. F., WHITE, P., MARBLE, A., and BAILEY, C. C. (1947). "The Treatment of Diabetes Mellitus", p. 54. Lea and Febiger, Philadelphia.
- MCCULLOCH, J. C., and PASHBY, T. J. (1948). "Diabetic Retinopathy", given before the Section of Ophthalmology of the Toronto Academy of Medicine, January 12, 1948.
- OPIE, E. L. (1901). *J. exp. Med.*, **5**, 527.
- WAITE, J. H. and BEETHAM, W. P. (1935). *New Engl. J. Med.*, **212**, 367; 429.
- WAGENER, H. P., DRY, T. J. S., and WILDER, R. M. (1934). *Ibid.*, **211**, 1131.