Brit. J. Ophthal., 35, 189.

COMMUNICATIONS

RETINAL MICRO-ANEURYSMS IN THE NON-DIABETIC SUBJECT*

BY

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THE present theories of the histogenesis of retinal micro-aneurysms are largely based upon the association of these lesions with the diabetic state and, in investigating the validity of these arguments, it is clear that it is first essential to know whether micro-aneurysms are in fact confined to this disease, and, if not, in what other conditions they may be found.

The pioneer work of Ballantyne and Loewenstein (1943) had led us to believe that such lesions were only rarely to be found apart from diabetes, and this opinion was supported by Friedenwald (1948), who stated that they were occasionally to be seen in cases of retinal vascular disease in non-diabetics, but that these were quite rare, and that not more than two or three of them were to be found in a whole retina. More recently Friedenwald (1950) has investigated 76 diabetic retinae and a " somewhat larger number " of non-diabetic cases. In the latter group he succeeded in finding only one case in which there was an " appreciable number " of capillary aneurysms. He examined thirteen cases of hypertensive retinopathy, of which three showed one or two isolated capillary aneurysms, apparently related to some localized tissue injury. No capillary aneurysms were seen in the retinae of elderly arteriosclerotics without diabetes, whether retinitis was present or not, and Friedenwald concluded that the capillary aneurysm is not a manifestation of arteriosclerosis, malignant hypertension, or arteriolar hyaline degeneration.

In the course of our studies in diabetic retinopathy at this Institute, some reports upon which have already been published (Ashton, 1949; 1950a, b, c), it was decided some 18 months ago to examine a large number of non-diabetic retinae for evidence of micro-aneurysms. A paper was read at the XVI International Congress of Ophthalmology in which some of the findings were incorporated ; since then more cases have been investigated, and it is now possible to present a more complete report.

* Received for publication December 22, 1950.

METHODS

The investigation involved the examination of 336 eyes and is divided into two parts:

(1) EYES REMOVED AT OPERATION.—In this group 162 eyes were examined. After removal, each eye was immediately placed in a vacuum flask containing carbon dioxide snow and sent direct to the laboratory. In 135 cases the retinae were removed and stained by the PAS (McManus) technique; the remaining 27 were examined by the injection method, reported in a previous publication (Ashton, 1950).

(2) EYES REMOVED *POST MORTEM*.—In this group 174 eyes taken from 88 unselected cadavers of non-diabetic persons were examined by the injection method, and the clinical histories were consulted only after the results had been recorded.

In diabetes there is a close association between Kimmelstiel-Wilson's disease and retinopathy, and aneurysmal dilatations may be seen in both the retinal capillaries and the glomerular tufts. A piece of kidney was therefore taken from each cadaver to ascertain whether non-diabetic retinal micro-aneurysms were similarly associated with such changes in the glomeruli.

As will be seen from the following analysis of the results, the staining method, though frequently giving perfect differentiation, is, at least in our hands, an unreliable method, especially in pathological material where the presence of an adherent vitreous, frequently containing exudate which stains intensely, obscures the finer vessels. It is not intended to underestimate the value of the PAS staining method for it is unsurpassed for studying microscopical changes in the vessel walls, but, in our experience, the injection technique is superior in the search for and location of micro-aneurysms and other vascular irregularities in the whole retina. The injection method has the added advantage that red pigment can be injected into the artery and black into the vein so that the two vessels can be more easily differentiated: no shrinkage occurs as in the staining technique and the whole retinal vascular structure can be seen with remarkable clarity. The question arises, however, whether it is possible to produce aneurysms artificially by forcing injection fluids into the delicate retinal vessels. This point has been fully investigated by using old and degenerate eyes, by utilizing high pressures, and by comparing the uninjected with the injected eye. *We are satisfied that it is not possible to produce aneurysms as an artefact by the injection method.*

RESULTS

(1) EYES REMOVED AT OPERATION

Cases Examined by Staining Methods

Number of Cases	Vessels not Visible	No MAs*	MAs Present
135	67	49	18

* MAs denotes micro-aneurysms.

Thus by the staining method the capillaries were not sufficiently well differentiated for the exclusion of aneurysm formation in about 50 per cent. of the cases. Of the 67 cases in which adequate examination was possible, eighteen (26.8 per cent.) showed micro-aneurysms. The findings are set out in detail in Table I.

TABLE I
EYES REMOVED AT OPERATION EXAMINED BY STAINING

Case No.	Age	B.P.	MAs	Histological Diagnosis
1	—	—	One or two	Chronic glaucoma
2	54	—	A few	Thrombotic glaucoma
3	66	—	A few	Thrombotic glaucoma
4	79	—	One or two	Chronic uveitis Secondary glaucoma
5	82	—	+ + +	Thrombotic glaucoma
6	62	—	One or two	Chronic uveitis Secondary glaucoma
7	66	166/84	+	Chronic uveitis Secondary glaucoma
8	83	—	One or two	Thrombotic glaucoma
9	80	—	+	Thrombotic glaucoma
10	—	—	+ + +	Thrombotic glaucoma
11	72	125/60	+ + +	Chronic uveitis Secondary glaucoma (Trephine operation)
12	43	—	One or two	Chronic uveitis Secondary glaucoma
13	76	—	+ +	Chronic uveitis Secondary glaucoma
14	—	—	+ +	Chronic uveitis Secondary glaucoma
15	15	124/74	One or two	Injury Chronic uveitis Secondary glaucoma
16	—	—	+	Thrombotic glaucoma
17	78	—	+	Cataract extraction Sympathetic ophthalmia
18	—	—	+	Thrombotic glaucoma

Cases Examined by the Injection Method

Number of Cases	Vessels not Visible	No MAs	MAs Present
27	5	10	12

Thus by the injection method only 18.5 per cent. were unsatisfactory, and when it is remembered that some of these eyes were completely disorganized with total retinal detachment and atrophia bulbi it will be realized that the injection technique, when searching for vascular irregularities, is far superior to the staining method. Of the 22 cases in which adequate examination was possible, twelve (54.5 per cent.) showed micro-aneurysms. The findings are set out in detail in Table II.

TABLE II
EYES REMOVED AT OPERATION EXAMINED BY INJECTION

Case No.	Age	B.P.	MAs	Histological Diagnosis
1	56	260/130	+ +	Thrombotic glaucoma
2	64	110/70	One or two	Chronic uveitis Detached retina
3	68	140/70	A few	Chronic uveitis Secondary glaucoma
4	62	—	+ + +	Thrombotic glaucoma
5	72	180/90	+	Choroidal melanoma involving the disk
6	67	190/100	+ + +	Chronic glaucoma
7	1½	—	One or two	Coats' disease
8	9	—	+	Old perforating wound Chronic uveitis
9	40	130/80	+ + +	Old perforating wound Secondary glaucoma
10	1	—	+ + (in tumour only)	Retinoblastoma
11	45	—	+	Perforating corneal wound Chronic uveitis Secondary glaucoma
12	63	—	+	Perforating corneal wound Chronic uveitis

Tables I and II taken together show the following percentage of positive results:

Cases examined 162.
Vessels satisfactorily seen 89.
Micro-aneurysms present 30 (33 .7 per cent.).

Disease	Number	Percentage
Thrombotic glaucoma	10	33.3
Chronic uveitis ... ... Secondary glaucoma	10	33.3
Perforating injury ... ... Uveitis. Glaucoma...	4	13.3
Chronic glaucoma	2	6.6
Perforating injury ... ... Sympathetic ophthalmia	1	3.3
Coats' disease	1	3.3
Choroidal melanoma	1	3.3
Retinoblastoma	1	3.3

In each of the above cases the clinicians in charge confirmed the absence of diabetes and reported that no micro-aneurysms were to be seen in the fundus of the remaining eye. Case 9 (Table II) was of particular interest and will be described separately.

Case 9 (Table II).—Male aged 40 years (patient of Mr. A. G. Leigh), sustained a perforating injury of the right cornea in 1933 following an explosion in a chemical laboratory. Seventeen years later there was bare perception of light in this eye with posterior synechiae and raised tension, and it was enucleated for cosmetic reasons. Apart from the eye the patient was in perfect health; his blood pressure was 130/80 and the urine was free from sugar and albumen. The injected retina showed a large number of micro-aneurysms scattered throughout the fundus, arising from the venous side of the capillary network and from the veins themselves; they were predominantly of the beaded type but many were indistinguishable from the unilateral kind seen in diabetic retinopathy (Figs 1 and 2). The histological diagnosis was perforating corneal wound with band-shaped opacity, traumatic cataract, and secondary glaucoma.

(2) EYES REMOVED *POST MORTEM*

All Retinae Investigated by the Injection Method.

Number of Cases	Unsatisfactory	No MAs	MAs Present
88 (176 eyes)	3	56	29

FIG. 1.—Case 9 (Table II), injected retina from a male aged 40, who sustained a perforating injury of the cornea 17 years before enucleation. Multiple micro-aneurysms may be seen on venous side of capillary network. They are predominantly of the beaded variety. Unstained. x 42

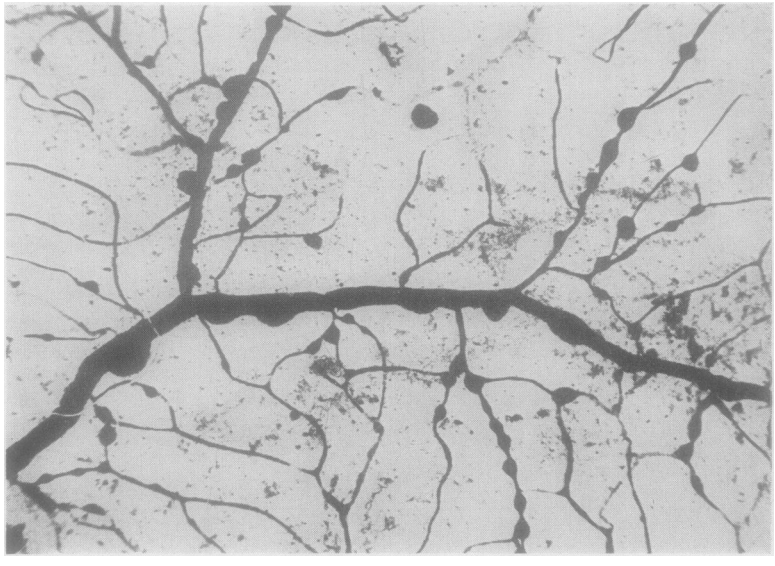

FIG. 2.—Case 9 (Table II), same retina as in Fig. 1, showing involvement of venules as well as capillaries. Note that micro-aneurysms do not arise predominantly at capillary bifurcations. Unstained. x 42

Thus of the 85 successful cases, 29 (34.1 per cent.) showed micro-aneurysms; the findings are set out in detail in Table III (pp. 196-8). Unfortunately *ante-mortem* ophthalmological reports were available in only a few of these 29 cases. Obviously nothing can now be done to replace this deficiency in our data, but in order to analyse the findings, the cases have been arbitrarily divided into two groups:

(1) Where gross fundus changes were likely to have been apparent during life.

(2) Where no gross fundus changes were likely to have been apparent during life.

Group 1.—Six cases (13, 25, 29, 60, 83, 87) fell into this group. Cases 13 and 25 were examples of venous thrombosis and chronic uveitis respectively, and since we have already demonstrated the association of these conditions with aneurysm formation they will not be further discussed. Case 29 was one of hypertension with polycystic disease of the kidneys, the fundus picture very closely resembled diabetic retinopathy, but since the urine was reported green to Benedict's reagent, this case must be rejected from the analysis. The remainder (60, 83, and 87) were all cases of malignant hypertension and showed features of particular interest which will be discussed separately.

Case 60.—Male aged 60 years, first seen in June, 1950, by Dr. A. L. Jacob, who kindly provided the clinical history. His first complaint was of defective vision about two months previously, but he had apparently been dyspnoeic for a considerable time. On examination he was extremely ill and mentally confused, and a full history could not be obtained. He was found to be suffering from severe heart failure and was admitted to hospital the same day. The blood pressure at that time was 180/120 and the fundus showed severe hypertensive retinopathy. The urine was examined on several occasions; there was heavy albuminuria but no sugar. The blood urea was 400 mg./100 ml. He died 5 days after admission and it was subsequently found that he had attended Moorfield's Hospital, under Mr. Doggart, in the previous February. The fundus reports at that time show that both disks were swollen, there were haemorrhages and exudates with gross spasm of the arteries. His blood pressure was 240/150 and a diagnosis of malignant hypertension was made.

Kidneys.—Sections showed polycystic disease, severe arterio-sclerosis, glomerular hyalinization, and fibrinoid necrosis in a few of the afferent arterioles. The picture was that of malignant hypertension superimposed upon a polycystic disease of the kidneys.

Retinae.—Both retinae were injected with red in the arteries and black in the veins; they showed haemorrhages, superficial white fluffy exudates and deep punctate exudates. There were vascular irregularities and multiple micro-aneurysms, apparently confined to the venous side of the capillary network and situated mainly in the posterior polar region. The right retina was stained with Scharlach red and mounted flat. The left retina was sectioned in carbowax and stained with Scharlach red, haematoxylin, and PAS (McManus). The preparations showed that the superficial exudates contained conglomerations of cytoid bodies. The deep exudates, situated in the outer molecular layer, stained positively with PAS and contained considerable quantities of fat, both free in the exudate and within macrophages. Fat-containing

TABLE III
EYES REMOVED *POST MORTEM* EXAMINED BY STAINING

Case No.	Sex	Age	B.P.	Injected Retina	Cause of Death
13	F	68	220/80	Right: MAs + + +, localized to one vein ? old thrombosis	Carcinoma of ovary Secondary carcinoma of pleura and pericardium Hypertension
19	M	74	150/90	Left only One or two large peripheral MAs	Malignant hepatoma Bronchopneumonia
20	M	65	130/78	A few peripheral MAs seen in both retinae	Perforated gastric ulcer Peritonitis
25	M	54	120/80	Right only Retinal detachment Retinitis proliferans Scattered MAs + (bilateral uveitis)	Chronic bronchitis Suppurative mediastinal adenitis
29	M	66	180/120	Right : multiple MAs + Loop formation. Intra-retinal new vessels Pathologically closely resembles diabetic retinopathy	Gangrene of right leg Chronic bronchitis Polycystic disease of kidneys
36	F	52	130/80	A few MAs in both retinae, mainly peripherally situated	Congestive heart failure Auricular fibrillation
38	F	59	120/90	Left: MAs + in one section only Right: normal	Acute bronchitis Chronic asthma
40	F	79	140/30	Both retinae showed MAs + scattered throughout the retinae particularly peripherally	Renal insufficiency Bilateral pyonephrosis Cardiovascular degeneration
42	M	71	135/90	One or two small peripheral MAs in both retinae	Cerebral thrombosis Purulent bronchitis
43	M	67	120/70	Both retinae show MAs + scattered throughout the fundi, particularly peripherally	Bronchiectasis Purulent bronchitis
46	M	52	90/70	Left: scattered small MAs Right: MAs + on the temporal side peripherally	Carcinoma of bronchus Chronic bronchitis Congestive heart failure
48	M	69	135/80	Right: 3 small MAs seen peripherally Left: normal	Perforation of oesophagus. Transthoracic operation for gastric carcinoma
50	M	42	120/60	Both retinae show loop formation and a few scattered MAs	Bronchopneumonia Extra-renal uraemia Pyloric ulcer

TABLE III—*continued*

Case No.	Sex	Age	B.P.	Injected Retina	Cause of Death
51	M	72	—	Right: one MA seen peripherally Left: normal	Carcinoma of bronchus Mediastinal secondaries Thrombosis of jugular vein
52	M	64	165/35	Right: beading and fusiform MAs on temporal side peripherally Left: infero-temporal region—one or two MAs seen peripherally	Acute bronchitis Aortic regurgitation Cardiac failure Pulmonary T.B.
54	M	27	100/?	Both retinae show one or two peripheral MAs	Haematemesis Peptic ulcer Patent I.V. septum
56	M	62	150/120	Right: beading only Left: beading and one or two peripheral MAs	Bilateral pulmonary tuberculosis
59	M	65	180/30	Right: one or two scattered MAs situated peripherally on the nasal side	Thoraco-abdominal gastrectomy Empyema
60	M	60	180/120	Both retinae show haemorrhages, exudates and multiple MAs (Reported in detail below)	Cardiac failure Hypertension Polycystic disease of kidneys
62	M	69	190/180	Right: in the equatorial zone there are several scattered MAs indistinguishable from the diabetic type. Beading and looping may be seen. Irregularities confined to the venous side Left: similar changes but less marked	Cerebral thrombosis Hypertension
64	F	70	260/110	Right: situated in the posterior fundus on the nasal side there is a collection of MAs with beading on the venous side Left: One large MA seen on the arterial side near the disk. Some looping present	Thrombosis of aorta Cardiovascular degeneration Paget's disease
69	M	75	120/80	Right: one or two scattered ? MAs and varicose loops	Carcinoma of prostate. Cardiovascular degeneration
72	F	73	185/80	Right: about 25 peripheral MAs seen Left: few scattered MAs seen peripherally	Carcinoma of breast Secondary carcinomatosis

TABLE III—*continued*

Case No.	Sex	Age	B.P.	Injected Retina	Cause of Death
74	M	72	230/140	Left: one or two scattered MAs	Cerebral haemorrhage Hypertension Coronary thrombosis
77	M	66	110/70	One or two scattered MAs and varicose looping in both retinae	Chronic bronchitis Cardiac failure
78	F	77	128/80	One or two peripheral MAs seen in both retinae. A small group of MAs at the equator in the right eye	Coronary occlusion
83	M	57	220/120	Both retinae show marked papilloedema and at the disk there is varicose looping and coil formation (Reported in detail below)	Malignant hypertension Cerebral haemorrhage Bronchopneumonia
84	F	61	—	Left: one or two MAs in posterior polar region. At the periphery on the nasal side there is a number of MAs, both of the diabetic and non-diabetic type—exudate surrounds some of them Right eye sectioned—no evidence of amyloid deposits	Chronic rheumatoid arthritis Amyloidosis Renal insufficiency
87	M	44	260/170	Both retinae showed varicose looping and coiling of capillaries at the papilloedematous disk. MAs present (Reported in detail below)	Malignant hypertension Uraemia

macrophages could also be seen in the inner layers of the retina around the capillaries, from which the fat appeared to be arising (Fig. 3). The micro-aneurysms were exactly similar to those seen in diabetes showing thickening of their walls with fat-containing exudate.

Case 83.—Male aged 57 years, was well until 4 months before admission to hospital in October, 1950, when he complained of dizziness and " falling down ". On admission he was mentally confused and incontinent of urine and faeces. The blood pressure was 220/120, the urine was free of albumen and sugar and the blood urea was 30 mg./100 ml. The fundi showed " narrowing of the arteries and exudates " (House Physician's report). He died 10 days after admission and the *post-mortem* diagnosis was malignant hypertension, cerebral haemorrhage and bronchopneumonia.

Kidneys.—Sections showed nephro-sclerosis. There was no evidence of arteriolo-necrosis and one may conclude that the malignant phase of the hypertension was still in its early stages.

Retinae.—Both retinae were injected with red in the arteries and black in the veins. The appearance of the flat preparations was remarkable. In both specimens there was marked papilloedema with a striking degree of varicose looping and corkscrew

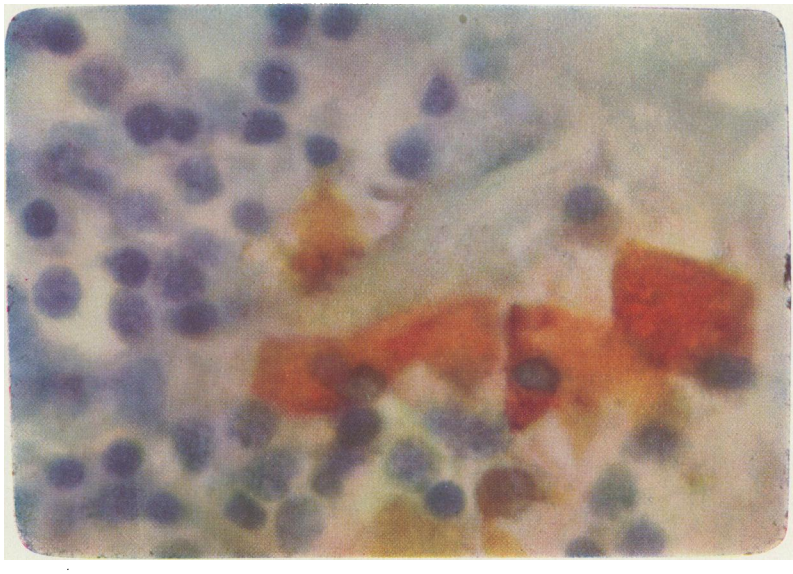

FIG. 3.—Case 60, left retina. The section shows fat-containing macrophages around a capillary vessel in a case of malignant hypertensive retinopathy.
Carbowax section. Scharlach red and haematoxylin.

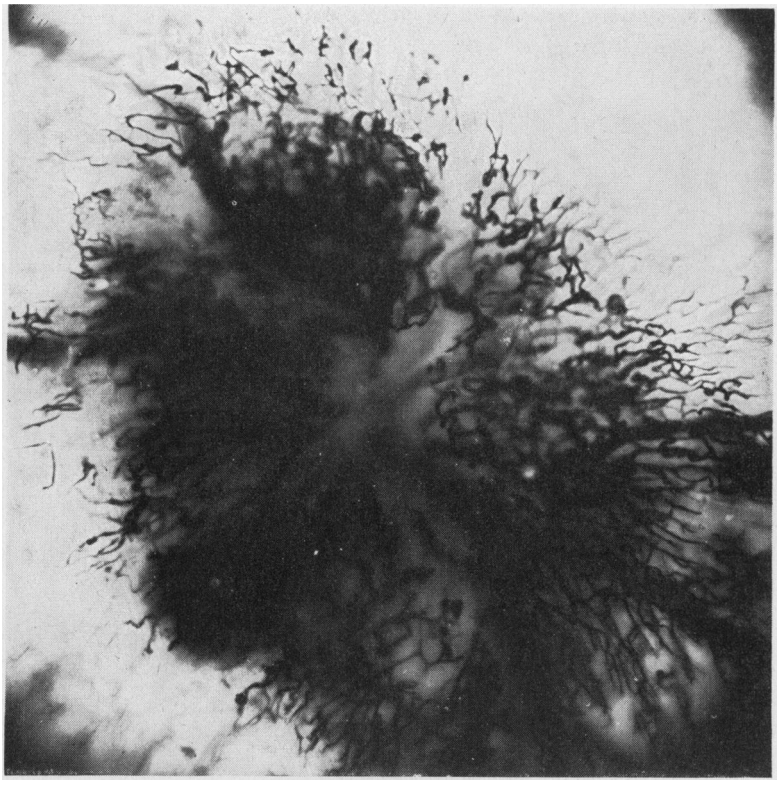

FIG. 4.—Case 83 (Table III, Group 1), malignant hypertension, left retina injected with red and black. Marked papilloedema with a striking degree of varicose looping and corkscrew coiling of the capillaries and venules in peripapillary region. These changes are localized and well demarcated. Unstained. x 26

coiling of the capillaries and venules in the peripapillary plexus. The area in which these changes were noted was well demarcated (Fig. 4) and corresponded to the anatomical distribution of the central plexus described by Michaelson and Campbell (1940). The peripapillary changes were most marked in the deepest layers of the plexus (Figs 5 and 6, overleaf). In both retinae a few small aneurysms were seen immediately below the disk on the venous side of the capillary network. The left retina was stained with Scharlach red, and fat globules were seen in close relation to the aneurysms (Fig. 7, overleaf). No arterial or arteriolar aneurysms were found.

Case 87.—Male aged 44 years, a two week's history of breathlessness and oedema of the ankles before the patient was admitted to hospital, where he was found to be suffering from malignant hypertension and uraemia. The blood pressure was 260/170, the blood urea 280 mg./100 ml., and the urine was reported free of albumen and sugar.

Fundus.—Bilateral papilloedema and haemorrhages. A left macular haemorrhage caused loss of vision. The patient developed pericarditis and bronchitis and died 6 days after admission. An autopsy confirmed the clinical diagnosis.

Kidney.—Sections showed a typical malignant nephrosclerosis with severe hyperplastic arteriosclerosis and arteriolonecrosis of the vasa afferentia of the glomeruli.

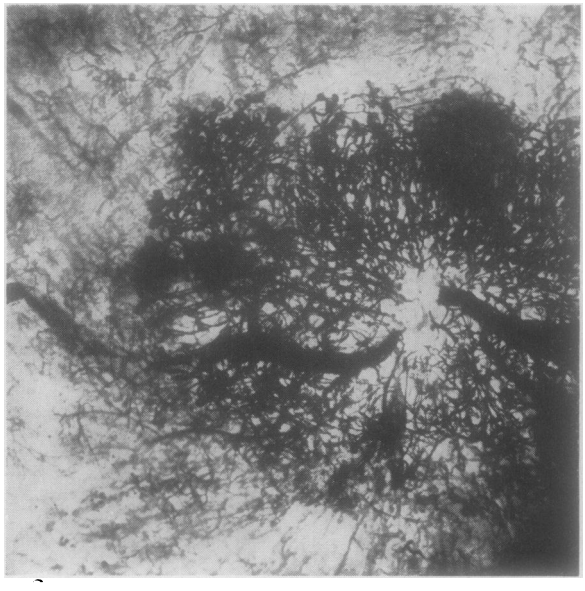

FIG. 5.—Case 83 (Table III, Group 1), malignant hypertension, left retina, injected, cleared, and mounted in Canada balsam. Photograph taken from posterior aspect of disk shows marked engorgement, looping, and coiling of deep vessels in peripapillary plexus. Same case as Fig. 4. Unstained. x 20

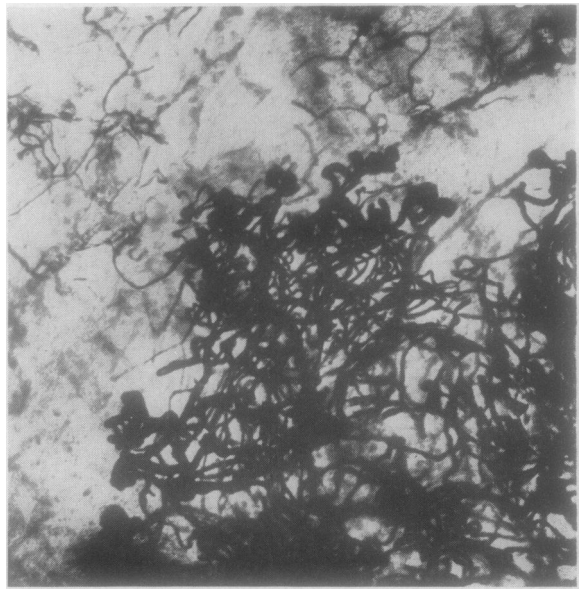

FIG. 6. — High-power view of Fig. 5, capillary changes end abruptly at margin of the peripapillary plexus, this distribution corresponds to area of papilloedema. Unstained. x 54

Retinae.—The right eye was not injected: it was cut open transversely through the ora serrata and the fundus examined under the stereoscopic microscope. There was marked papilloedema and yellowish white exudates at the macula and in the maculopapillary area. Scattered flame-shaped haemorrhages were seen in the region of the disk on the temporal side and equatorially at 5 o'clock and 11 o'clock. The upper temporal branch of the retinal artery was sheathed with a number of small white dots.

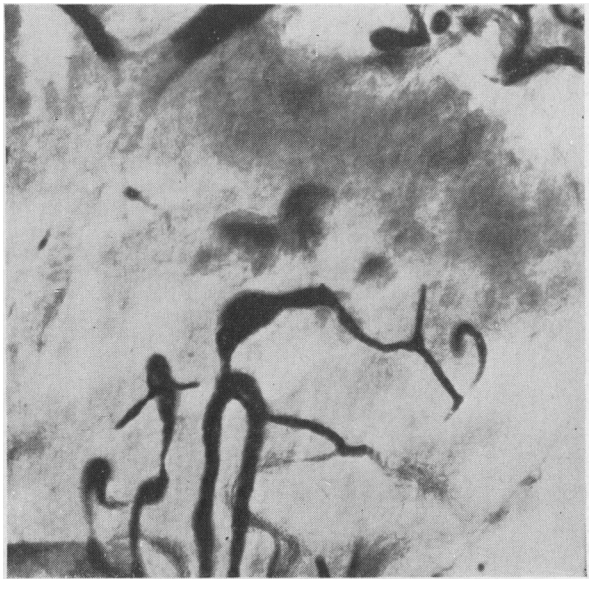

FIG. 7.—Case 83 (Table III, Group 1), malignant hypertension, left retina showing fatty exudates around a capillary micro-aneurysm. Two large globules of fat appear immediately above the aneurysm. Injected. Scharlach red. x 148

Fluffy white exudates were seen near the disk on the temporal side. A drawing was made of the fundus and serial sections were cut of the specimen: half in celloidin and half in carbowax.

Serial Sections of Right Eye (celloidin).—The fluffy exudates were seen to consist of aggregations of cytoid bodies. Superficial and deep haemorrhages were seen in the retina and there were a few haemorrhages in the choroid. Both the retinal and choroidal vessels showed extreme arteriosclerosis and in the choroid some arterioles showed arteriolonecrosis, especially those adjacent to the haemorrhages. Extensive exudates were seen in the outer molecular layer. Carbowax sections stained with Scharlach red showed only a few lipoid granules in scattered macrophage cells, thus confirming the view that the oedema fluid in malignant hypertension is at first albuminous (Semple, 1911). No lipoids were seen in the cytoid bodies.

Left Eye.—Injected with red in the arteries and black in the veins. The flat preparation showed varicose looping, corkscrew coiling (Fig. 8), and scattered micro-aneurysm formation in the capillaries around the disk. The appearances were similar to those found in Case 83, but the area affected was less well differentiated. There was also a group of micro-aneurysms situated equatorially at 2 o'clock; they were of the beaded variety and confined to the venous side of the capillaries (Fig. 9). One larger aneurysm, surrounded with exudate, was seen on an arteriole (Fig. 10). The retina was studded with fine white dots, which were apparently fat-containing macrophages (Fig. 11). No peripheral micro-aneurysms were seen. Cytoid bodies were present near the disk on the temporal side.

Group 2.—Of the cases examined, 79 fell into this group and micro-aneurysms were found in 23 (29 per cent.), which can be sub-divided as follows:

(*a*) Aneurysms confined to the peripheral part of the retina, ten cases = 43.5 per cent. (19, 20, 36, 42, 48, 51, 52, 54, 56, 72).

(*b*) Aneurysms scattered throughout the retina, nine cases = 39.1 per cent. (40, 43 46, 50, 59, 69, 74, 77, 78).

(*c*) Aneurysms confined to the posterior part of the retina, four cases = 17. 4 per cent. (38, 62, 64, 84).

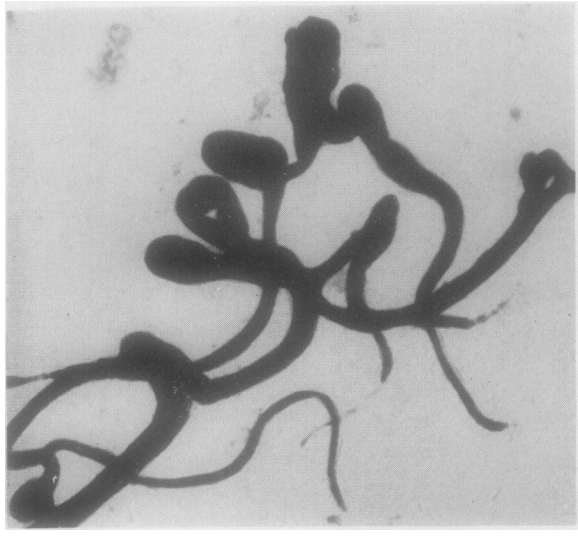

FIG. 8.—Case 87 (Table III, Group 1), malignant hypertension. High-power view of varicose looping and coiling seen in capillaries in region of disk, as shown also in Case 83, Fig. 6. Injected. Unstained. x 221

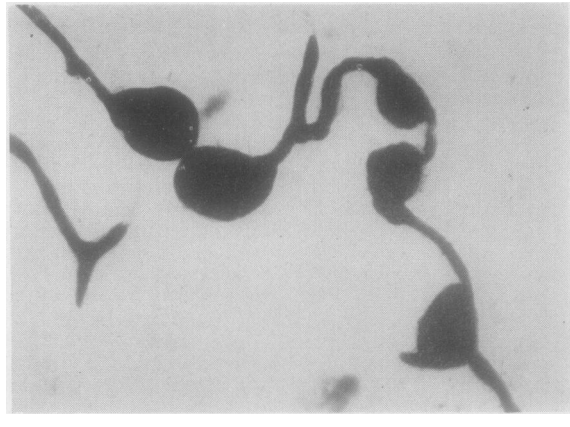

FIG. 9.—Case 87 (Table III, Group 1), micro-aneurysms in a case of malignant hypertension, lesions situated on *venous* side of capillary network. Injected. Unstained. x 221

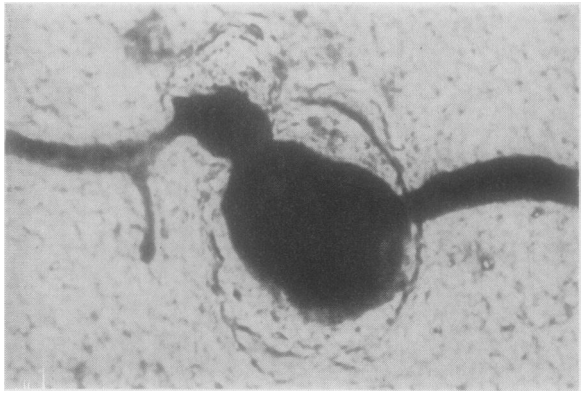

FIG. 10.—Case 87 (Table III, Group 1), malignant hypertension, left retina showing large micro-aneurysm, surrounded with exudate and situated on *arterial* side of capillary network. Injected. Unstained. x 295

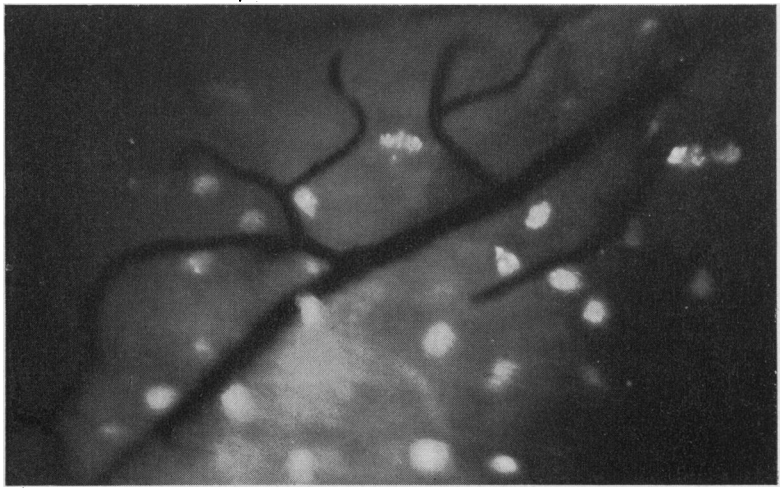

FIG. 11.—Case 87 (Table III, Group 1), malignant hypertension, left retina, injected with Indian ink and mounted flat, unstained. Note presence of fat-containing macrophages scattered throughout retina. Dark-ground illumination. x 120

It will thus be seen that in nineteen (24 per cent.) of the 79 *post-mortem* cases, in which no eye disease was suspected and in which no gross ophthalmoscopical findings were to be expected in life, there were micro-aneurysms in the peripheral part of the retina, and in ten of these they were confined to the periphery of the fundus. As would be expected in the examination of *post-mortem* material the ages of the patients ranged between 50–80 years; only two cases were under 50. In the majority of cases the blood pressure was within normal limits. There was no history of diabetes in any of the 23 cases and the urine was reported free from sugar. The causes of death were so diverse that it is not possible to correlate the *post-mortem* findings with the presence of micro-aneurysms. Early in the investigation it was thought that micro-aneurysms might result from the prolonged venous engorgement of chronic cardiac or pulmonary disease, but the negative cases (not reported in detail here) show that aneurysms are as commonly absent as present in these conditions. In the majority of cases the micro-aneurysms were very small and mostly of the beaded variety and were situated on or near the venous arcades at the periphery of the retina. Nevertheless aneurysms were frequently seen, with exudate around them, which were indistinguishable from the diabetic type, as for example in Case 84 in which there was renal insufficiency, with amyloidosis and chronic rheumatoid arthritis. Sections of the eye in this case showed no abnormality and there were no amyloid deposits within it (Figs 12 and 13, overleaf).

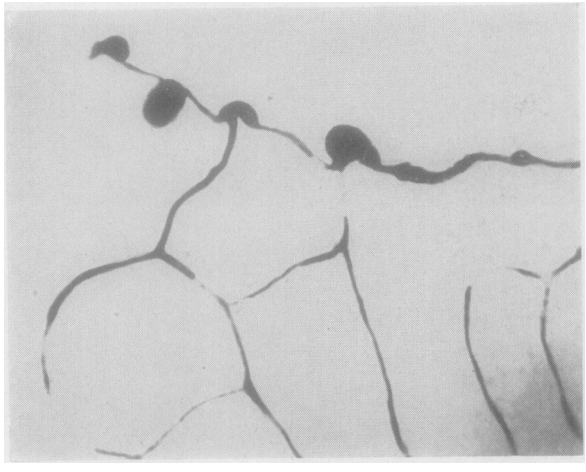

FIG. 12.—Case 84 (Table III, Group 2), rheumatoid arthritis and amyloidosis, sections of the eye showed no abnormality. Left retina, injected with Indian ink, shows aneurysmal dilatations situated on venous side of capillaries at extreme periphery of retina. Unstained. x 110

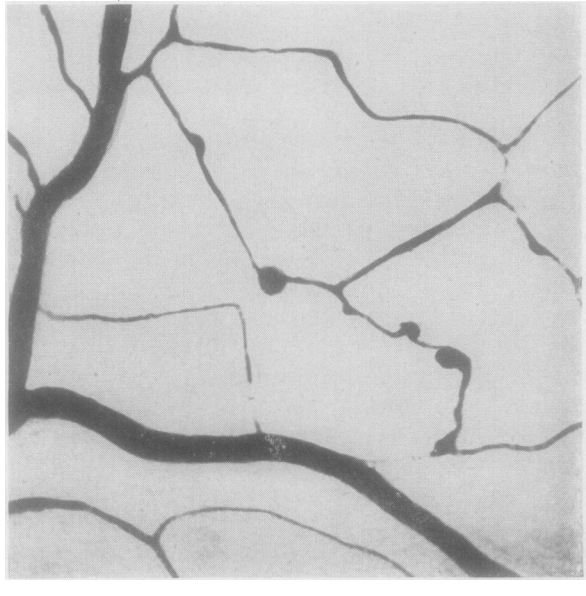

FIG. 13.—Another part of the retina from the same case shown in Fig. 12. Note that the aneurysms are small and not particularly related to the capillary bifurcations. These are typical examples of the type of aneurysm found commonly at the periphery of the retina in the " normal " eye. Unstained. x 110

Kidneys.—In none of the 23 cases did the kidney sections show evidence of intercapillary glomerulosclerosis. In Case 84, the glomeruli contained amyloid deposits but the others showed nothing more than benign nephrosclerosis of varying degrees of severity. Aneurysmal dilatations were not seen on the glomerular capillaries in any case, but the kidneys were not subjected to any special injection techniques.

DISCUSSION

In this analysis the finding of even one or two micro-aneurysms in a whole retina has not been neglected, and this fact will explain in

some degree why the incidence of the lesions in our series of cases is much higher than in those already reported. Friedenwald (1950) states that among his non-diabetic cases there was only one " in which there was an appreciable number of capillary aneurysms ", and Wexler and Branower (1950) have noted only those cases showing " significant capillary lesions ": neither paper states, however, the number or size of aneurysms which should be regarded as appreciable or significant, but it follows from these authors' statements that, in their view, a certain number or size of aneurysms can be regarded as within normal limits. It has seemed to us that in order to discover the cause of these lesions it is premature at the beginning of the investigation to decide arbitrarily upon a significant number, for that is surely part of the purpose of the investigation itself. The number of lesions is probably related only to the severity and extent of the causative factors; indeed all the problems involved are as provocatively posed by one micro-aneurysm as by a larger number.

The finding of micro-aneurysms in the retina in such a high percentage of " normal " and pathological eyes is surprising and it is difficult to elaborate a single theory which will explain the histogenesis of these lesions in each of the conditions in which we now know them to occur. The findings will therefore be discussed in the same order as in the first part of this paper.

EYES REMOVED AT OPERATION.—It is clear from the analysis of these cases that micro-aneurysms occur commonly in the diseased eye, apart from diabetes, and are most frequently seen in venous thrombosis and chronic uveitis. It would appear that the change in the capillaries preliminary to aneurysm formation is a focal mural degeneration, which both in diabetes and malignant hypertension has been seen to involve the basement membrane described by Friedenwald. As elsewhere in the body, such a change leads to increased permeability of the vessel wall or to its rupture with the formation of petechial or ecchymotic haemorrhages, but in the retina there is an intermediate stage of aneurysm formation, which as far as is known is found almost exclusively in these vessels. The process of formation of aneurysms in thrombosis of the retinal vein is fairly clear: when the occlusion in the central or branch vein is sufficiently advanced to obstruct the flow of blood, there is a slowing of the blood stream and a dilatation of the veins above the obstruction, the resulting stasis, anoxia, and engorgement lead to vascular degeneration and aneurysm formation on the venous side.

In chronic uveitis the problem is less straightforward. It is probable, however, that the capillary degeneration and engorgement are secondary effects of the toxic products of the causative agent of the uveitis itself: the cuff of leucocytes which forms around the retinal vessels in acute and chronic uveitis is evidence that such a

secondary process exists. If there were an associated perforating injury the resulting fall in tension would further facilitate the formation of aneurysms by reducing the external vascular support, as in Case 9 (Table III). Why the process affects particularly the venous side of the capillary network is not known, indeed the same problem exists in diabetes, but it is further evidence of the greater vulnerability of the retinal veins to the toxic products of various inflammatory processes or other noxious agents.

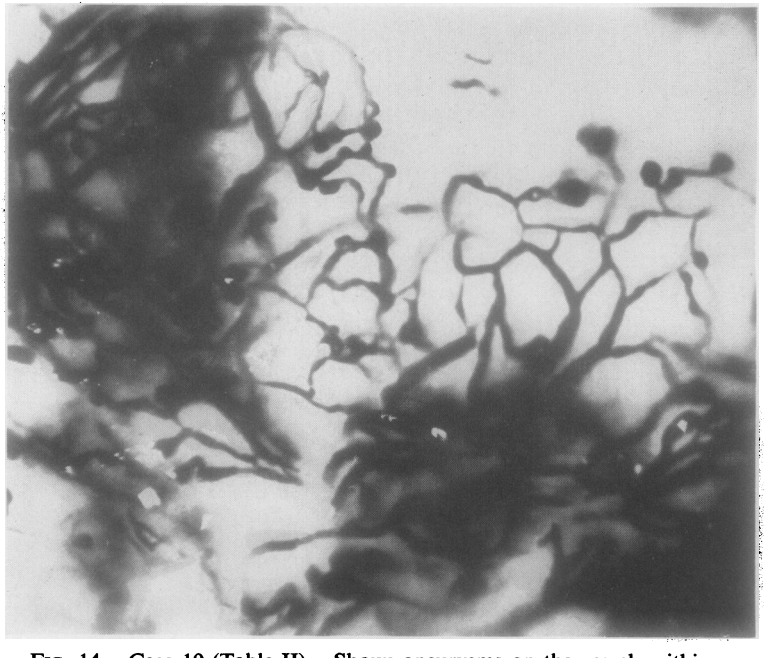

FIG. 14.—Case 10 (Table II). Shows aneurysms on the vessels within a retinoblastomatous growth. Injected Indian ink. x 45

Comment should be made upon the aneurysms seen in retinoblastoma (Fig. 14) and in choroidal melanoma. In the case of retinoblastoma, the aneurysms were confined within the neoplastic mass, while the vessels elsewhere in the retina were completely normal. It is, therefore, probably not comparable to aneurysm formation in other conditions, being merely an irregularity associated with abnormal vascular growth within the tumour: such lesions are seen also in the vascular neoplasia of angiomatosis retinae (Snell, 1925), in vascularization of the cornea (Cogan, 1949), as the "blood islands" of mustard gas keratitis (Mann, Pirie, and Pullinger, 1948), and in the vascular dysplasia of hereditary telangiectasis (Blackwood and others, 1949). In the case of the choroidal melanoma the growth was unusual in that it involved the

central vessels and so obstructed the venous flow. The aneurysms were not confined to the growth but were visible throughout the retina and the histogenesis of these lesions is analagous to those of thrombotic glaucoma. From the examination of other melanomata of the choroid it is known that retinal aneurysms do not usually accompany them.

EYES REMOVED *POST MORTEM*

Group 1.—Of this group only the findings in the three cases of malignant hypertension remain to be discussed. Each showed a few micro-aneurysms on the venous side of the capillary network with fatty degeneration of the vessel wall, exudates, cytoid bodies, and fat-containing macrophages. Indeed, the main morphological features were very similar to those seen in diabetic retinopathy, from which, however, malignant hypertensive retinopathy differs in some details. In malignant hypertension the emphasis of the venous change is in the peripapillary region, aneurysms are smaller and fewer, and may be arteriolar, and cytoid bodies are more frequent. In Case 87 a large aneurysm surrounded with exudate was seen on an arteriole (Fig. 10).

It is necessary here to refer to the recent paper of Wexler and Branower (1950), who have reported their findings in the retinae of forty patients who had died from hypertensive vascular disease; 29 of them were benign and eleven malignant hypertensives. In every case of malignant hypertension sacculation and dilatation of the arterial capillaries with focal reduplication of the basement membrane at the point of sacculation were found. The lesions closely resembled the micro-aneurysms seen in diabetic cases but the lesions were limited to the arterial side of the capillary circulation, in contradistinction to the picture in diabetes, where the lesions are predominantly on the venous side. It should be pointed out, however, that it is not always easy to be certain from a stained flat preparation that such lesions are in fact confined to the arterial side of the capillary network, and it is possible that these authors may have been mistaken on this point. It may be true that in some cases the lesions are predominantly arterial, but in our three cases examined by injection of the vessels with red and black, the venous side of the capillary network was also heavily involved and micro-aneurysms, coils, loops, and beading were all to be seen on the venous side. Nor is this surprising when one considers the probable histogenesis of aneurysms in this condition. As Elwyn (1944) convincingly asserted in considering the work of Ricker (1924), the chronic arteriospasm leads to dilatation of the pre-arterioles, capillaries, and post-capillary venules, and vascular degeneration results from the sub-oxidation and sub-nutrition of the vessel walls themselves. One would therefore expect to find aneurysm formation in each of these

terminal units, and whether the venous or arterial side is the more heavily affected may depend upon the duration of the arteriospasm. Wexler and Branower (1950) further state that

> while these lesions probably result in capillary stasis, no evidence was found to indicate that they are responsible for the papilloedema, haemorrhages or exudates;

but if the above theory of histogenesis is correct, it is clear that the micro-aneurysm itself is merely an expression of the capillary stasis and vascular degeneration which precede its formation, and the same is true of the haemorrhages and exudates. There is still considerable difference of opinion as to the cause of papilloedema in malignant hypertension; many ophthalmologists, however, are confident that it is due to increased intracranial pressure and our finding of varicose looping and corkscrew coiling of the capillaries and venules in the peripapillary plexus of Michaelson and Campbell (1940) lends support to the view that there is such an impediment to the venous return beyond the disk, the effects of which appear to fall most heavily upon the peripapillary vessels, particularly in the deeper layers.

Group 2.—The finding of retinal micro-aneurysms in 29 per cent. of post-mortem cases in which no eye disease was suspected, and in which no gross ophthalmological findings were to be expected in life, is an indication of the surprising frequency of these lesions. Indeed, *apart from vascular sclerosis, the occasional capillary micro-aneurysm is the commonest pathological lesion in the retina.* In about half the cases the lesions were found to be confined to the extreme periphery of the field. They are usually very small and few in number, and may either be of the beaded variety, or arise from one side of the vessel wall, or develop from the adhesion of varicose loops; the last two types are characteristic of diabetes. They occasionally occur at the capillary bifurcation (Figs 12 and 13) but do not arise there particularly: indeed, in our experience the capillary junction is not the site of predilection for any type of retinal micro-aneurysm. On the other hand, Friedenwald (1950), believes the bifurcation to be the most frequent location of aneurysms, and has suggested that this may be due to a local anatomical weakness, as in the congenital aneurysms of the circle of Willis.

At the moment we have insufficient knowledge about this type of peripheral aneurysm to determine the cause of its origin or the reason for its anatomical distribution. As has been reported in a communication to the XVI International Congress (Ashton, 1950c) the retinal vessels in old age do not necessarily show micro-aneurysms: none was found in 64 eyes from 32 cadavers in which the age groups ranged from 10 to 80, eleven being over 70 years of age. Our findings in benign hypertension are in complete accord with those of Friedenwald (1950) and of Wexler and Branower (1950); aneurysms appear to bear no direct relationship either to the age of

the patient or to the brachial blood pressure, but the majority of the diseases in which they occur develop in the older age groups.

This investigation has therefore shown that micro-aneurysms are common in the retinal capillaries, but it is to be remembered that the inquiry was of necessity confined to eyes which were obtainable for microscopical examination and it can be confidently prophesied that the lesion is even more common than we have found. No doubt careful clinical ophthalmoscopical observation will reveal them in an even wider variety of inflammatory and degenerative diseases, for one can expect them to occur in any condition which leads to prolonged sub-oxidation and sub-nutrition of the capillary wall and in any disease where there is a chronic inflammatory or toxic injury to the capillaries, particularly on the venous side. Thus one may expect to find them in long-standing untreated cases of pernicious anaemia and in the retinal periphlebitis of Eales' disease. It may be that the original finding of Ballantyne (1943), that

> many, if not most, of the so-called punctate haemorrhages characteristically seen in diabetic retinopathy are actually capillary aneurysms,

is equally applicable to retinal punctate haemorrhages in the non-diabetic subject.

The clinician will naturally require some explanation for the apparent discrepancy between the pathological frequency of these lesions, and the incidence of their clinical observation. It is, therefore, important to stress that the non-diabetic aneurysm is usually very small, ranging in size from 10 to 50 microns; furthermore they are frequently situated peripherally, where the retinal vessels, especially in their finest detail, are not readily seen ophthalmoscopically. In some of the conditions in which they occur, such as uveo-retinitis, there is no view or only a limited view of the fundus, and lastly, it is probable that when they have been visible they may have often been mis-interpreted as punctate haemorrhages.

In conclusion, although it is not the purpose of this paper to deal with diabetes, it may be useful to consider how these further facts reflect upon the problem of diabetic retinopathy, which still remains the condition in which micro-aneurysms are seen most frequently and in their greatest numbers and most advanced forms. The finding of micro-aneurysms in the posterior part of the fundus in thirteen of our 79 non-diabetic post-mortem examinations slightly modifies Ballantyne's dictum that when these lesions occur alone they represent the earliest unequivocal sign of diabetes. It is now clear that this is not true; nevertheless it remains a valuable diagnostic pointer.

Ballantyne (1946), in the careful work he has carried out on this subject, has described in detail the fatty changes to be found in the capillary walls, particularly in aneurysmal areas, and this has led some workers, notably Renard and Dhermy (1950), to attempt to

link these changes with the general lipoid disturbance known to occur in diabetes. Dragstedt (1940) has demonstrated a lipotropic hormone believed to be secreted by the alpha cells of the islands of Langerhans in the pancreas; he believes that the deficiency of this hormone is responsible for the anomalies in lipoid metabolism, and has shown by animal experiment that it not only influences a fatty liver but also fatty deposits in arteries and throughout the body. Renard and Dhermy (1950) conclude that this alteration in the lipotrophic function of the pancreas brings about the fatty changes in and around the retinal vessels producing the characteristic diabetic retinopathy. It is therefore of interest to note that exactly similar fatty degeneration of the vessels, with fat-containing exudates and macrophages, were seen in association with the micro-aneurysms of malignant hypertension, and were also seen in several of the other non-diabetic cases in which micro-aneurysms were found. Furthermore, as far as can be decided from microscopical examination, there is nothing to distinguish fatty degeneration in the vessels of the diabetic from that in the non-diabetic, and this fact casts doubt upon the arguments advanced by Renard and Dhermy (1950): it does not, of course, disprove their case for there is no reason to expect that endothelial fatty degeneration from differing causes should necessarily vary in appearance. Nevertheless, our experience leaves us with the impression that the differing features of micro-aneurysms, both in number and morphology, are more probably related to the acuteness or chronicity of their development and to the severity of the sub-oxidation and sub-nutrition to which the vascular wall is subjected, whether these factors are brought about primarily from a failure of the blood supply itself, as in malignant hypertension and thrombosis, or secondarily from a stasis of the circulation due to endothelial damage, as is probable in diabetes and chronic uveitis.

In short, although the precipitating factors differ, the subsequent pathological changes of engorgement, dilatation, varicose looping, beading, fatty degeneration, exudation, micro-aneurysm formation, and haemorrhage are part of the same process and are basically identical in all cases. Since we know that in favourable cases the ophthalmoscopical picture in malignant hypertension may be completely restored to normal after sympathectomy, the findings we have here described give grounds for the hope that when the causative factors in diabetic retinopathy are known, and a rational therapy instituted, the condition may prove, at least in its milder stages, to be equally reversible.

SUMMARY

(1) In order to ascertain the incidence of retinal micro-aneurysms in conditions other than diabetes the retinae of 336 eyes from 250 non-diabetic subjects have been examined by staining and injection

techniques. 162 of the eyes were removed at operation and 174 were obtained at 88 *post-mortem* examinations. The kidney was examined histologically in every *post-mortem* case. In the search for vascular irregularities the injection method was found to be far superior to the PAS (McManus) staining method.

(2) Of those eyes removed at operation where the retinal vessels could be clearly seen after staining or injection, one-third showed micro-aneurysms, and these were most commonly found in cases of thrombotic glaucoma and chronic uveitis, being particularly numerous in an eye with uveitis following a perforating injury. Aneurysms were also found within a retinoblastomatous growth and in the retina of a case of choroidal melanoma in which the growth had obstructed the venous outflow.

(3) Of the eyes removed *post mortem*, where the retinal vessels could be clearly seen after injection, about one-third showed micro-aneurysms. The findings in each case are reported in detail. Since ophthalmological reports were available in only a few cases, the *post-mortem* series was divided into two groups:

(*1*) Where gross fundus changes were likely to have been apparent during life,

(*2*) Where no gross fundus changes were likely to have been apparent during life.

Three out of the six in the first group were cases of malignant hypertension. The findings in each of the three retinae are described in detail. They showed micro-aneurysms on both the venous and arterial side of the capillary network, with fatty degeneration in the vessel walls, exudates, cytoid bodies, and fat-containing macrophages. Two of the cases in which a well-marked papilloedema existed showed a striking degree of engorgement, varicose looping, and corkscrew coiling of the capillaries and venules in the peripapillary plexus. The findings are not in accord with those of Wexler and Branower (1950), who found that aneurysms were confined to the arterial side of the capillary network in malignant hypertension.

In the second group, in which no eye disease was suspected and in which no gross ophthalmological findings were to be expected in life, retinal micro-aneurysms were found in 29 per cent. of cases. In about half, the lesions were confined to the extreme periphery of the field; they were small and few in number but often indistinguishable from the diabetic type of aneurysm. The cause of their origin and the reason for their anatomical distribution are unknown. There seemed to be no direct relationship between the aneurysm formation, the age of the patient, the brachial blood pressure, or the cause of death.

(4) Capillary aneurysm formation in the retina has thus been shown to be of frequent occurrence, and it is believed that, apart from vascular sclerosis, the occasional capillary micro-aneurysm is the commonest pathological lesion in the retina.

(5) The significance of these findings is discussed, with particular reference to the important problem of diabetic retinopathy.

I am most grateful to the surgeons of the Moorfields, Westminster and Central Eye Hospital for the provision of eyes removed at operation and for the kind co-operation of Dr. A. B. Bratton and his staff, Drs. C. C. Bryson, W. Peters, S. H. B. Robinson, and C. Raeburn, who have provided the *post-mortem* material; my thanks are also due to the many clinicians who have kindly supplied the clinical details of their cases.

To Sir Stewart Duke-Elder and Mr. E. F. King I am indebted for advice in the preparation of this paper.

I wish to thank Dr. P. Hansell for the photographs, Miss E. FitzGerald for clerical assistance, and my technicians, Messrs. G. E. Knight, A. McNeil, D. Bedford, and G. E. Sharman, for their valuble technical assistance.

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