Though no toxoplasma parasites have been discovered, and it is perhaps rather late to expect a positive finding, there can be no doubt concerning the diagnosis. The mother's negative serum-reaction is difficult to explain. It is conceivable that the child acquired the infection after birth, but this would appear highly improbable in view of the extremely early age at which the sight was thought to be abnormal, and the presence of developmental abnormalities such as gross persistence of pupillary membrane. The mother is now seven months pregnant. X-rays of the foetal skull show no abnormal calcification at present, but this next child will be examined for toxoplasmosis soon after birth.

My thanks are due to Dr. J. A. Dudgeon for performing the serological tests, and to Dr. B. R. D. Wilson for information regarding the general condition of the patient.

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VASCULAR CHANGES IN DIABETES WITH PARTICULAR REFERENCE TO THE RETINAL VESSELS

Preliminary Report *

BY

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RECENT advances in pathological and clinical studies of diabetes indicate that at least some of the more important complications of this disease may have a common underlying cause, namely, a vascular degeneration. There is already an extensive literature referring to retinopathy, intercapillary glomerulosclerosis, peripheral neuritis and generalised athero-sclerosis in diabetes; their inter-relationship has been repeatedly emphasised and it is suggested that they should be regarded as different manifestations of the same underlying pathology.

Dedicated to Professor J. Meller.

* Received for publication, May 9, 1949.

As long ago as 1921 Wagener and Wilder pointed out that retinopathy of a diabetic type was almost always complicated by vascular or renal disease, and in 1934 Wagener, Dry and Wilder studied 1,052 diabetic cases and noted the association of retinopathy with disease of the peripheral nerves, which occurred in 25 per cent. of all cases in which retinopathy was present. The possibility occurred to them that lesions like those observed in the retina may also arise in relation to the peripheral nerves, and they further suggested that similar lesions affecting the vasa vasorum of the larger arteries might contribute to the atherosclerosis of those vessels, which occurs so frequently among diabetic patients at an earlier age than is common among persons who are not diabetic.

In 1936 Kimmelstiel and Wilson described the deposition of a hyaline material in the intercapillary connective tissues of the glomeruli of the kidney, and they were surprised to find, on reviewing the clinical data, that there was a previous history of diabetes in all their cases except one. They termed the lesion intercapillary glomerulosclerosis. Allen (1941), in an attempt to establish the significance of the renal lesion, carried their work to a further stage, and reported the examination of the kidneys from 105 consecutive patients with diabetes, 100 consecutive non-diabetic patients with hypertension, 100 consecutive non-diabetic patients without hypertension, and 34 patients with glomerulonephritis; the kidneys were studied with a variety of special stains, principally from the point of view of glomerular change. A characteristic focal glomerular hyalinisation of the type described by Kimmelstiel and Wilson was found in 33 per cent. of diabetic patients over the age of 40. The diabetic lesion was easily distinguishable from the glomerulosclerosis of nephrosclerotic kidneys from non-diabetic persons and from the glomerular hyalinisation of glomerulo-nephritic kidneys, but he regarded the diabetic lesion as a focal intramural glomerulosclerosis rather than an intercapillary hyalinisation as had hitherto been considered. The lesion was offered as the most reliable criterion available for the histological diagnosis of diabetes mellitus in cases over the age of 40. Bell (1942) considered the nodular type of glomerular lesion as almost pathognomonic for diabetes.

Henderson *et al.* (1947) found intercapillary glomerulosclerosis in 19·5 per cent. of 313 diabetic patients on whom necropsies were performed. That the lesion is not completely specific is shown from the fact that it was also found in 12·3 per cent. of 81 cases of glomerulo-nephritis and in 5·2 per cent. of 134 cases in which death was due to hypertension and its compli-

cations. Severe lesions, however, were by far the most frequent in cases of diabetes. He concluded that although intercapillary glomerulosclerosis cannot be diagnosed clinically with complete certainty, it should be strongly suspected in patients who have diabetes mellitus of long standing associated with albuminuria, hypertension, renal insufficiency and diabetic retinopathy; he adds that the more advanced types of diabetic retinopathy are more or less regularly associated with this renal lesion. Kimmelstiel and Porter (1948), reviewing the accumulated experience since their first publication, stated, from a selection of statistics, that intercapillary glomerulosclerosis of the nodular type occurs approximately in 17 per cent. of all diabetics, and twice as often in women as in men. It is rare in the first two decades of life, maximum at the sixth decade, and then declines. Retinopathy occurs in 86 per cent. of cases with the advanced lesion.

In 1943, 1944 and 1945 Ballantyne and Löwenstein investigated diabetic retinopathy from the clinical and pathological point of view and came to the conclusion that it was a separate entity quite distinct from the retinopathy of hypertension. They reported upon observations of the unstained flat retina, examined in bulk, and of the retina stained in vertical and horizontal serial sections; they gave reasons for believing that the so-called punctate haemorrhages seen on ophthalmoscopical examination are in fact globular micro-aneurysms which occur, almost without exception, in the inner nuclear layer from the capillaries which link the more superficial capillary network in the nerve fibre layer with the deeper plexus at the outer boundary of the inner nuclear layer. They noted that these lesions may be a source of haemorrhage by diapedesis or rhexis, and that they may undergo a process of thrombosis and cicatrisation. Their investigations, using Sudan and Scarlet R. staining, led them to conclude that these structures, and the other venous changes of which they are a part, are due to the combination of venous engorgement with localised fatty degeneration of the vessel wall, and they postulated an unknown selective circulatory chemical toxin as the probable aetiological factor. Ballantyne (1945) stated that micro-aneurysms may occur alone and seem to be the earliest unequivocal sign of diabetes. Elwyn (1941) is inclined to regard the lesions simply as capillary dilatations rather than true aneurysms, and he interpreted them as evidence of "prestasis" in the retina; he believed that, in a person who has hyperglycaemia of prolonged duration, the persistently high sugar level influences the terminal vessel units to produce dilatation which results in stasis with a state of chronic sub-nutrition and

deficient oxygen supply, with the consequent appearance of lipoids and hyaline material.

This brief review of the literature indicates that there is now ample evidence of a proclivity to a particular type of vascular degeneration in diabetes, particularly in long-standing diabetics in the older age-groups. As might be expected, and as Stocks (1944) and Joslin (1946) have shown, diabetics are living longer since the introduction of insulin, and the complications resulting from vascular disease are becoming correspondingly more frequent. Wagener (1945) reviewed the position of retinopathy in the light of modern knowledge, and he pointed out the serious fact that the frequency of its occurrence is increasing steadily. Croom and Scott (1949) have shown, however, from a clinical examination of 60 diabetics, that vascular complications are by no means inevitable even as late as 26 years after the onset of diabetes; nevertheless, a proper understanding of the pathology of the changes in the vascular system in the diabetic is clearly one of urgency and importance.

Little work has yet been done upon the correlation of the histological changes in the retinal vessels with those in the vessels elsewhere in the body. Ballantyne and Löwenstein confined their studies to the eye, and the renal lesions have been related only to the ophthalmoscopical appearances of the retina. An investigation has therefore been started in this department to compare the histopathological changes in the diabetic retina with disease in the vascular system generally. So far the post-mortem material from 24 diabetics has been examined, but since the eyes were not available for microscopical examination in three of the cases, only 21 are reported here. It is realised that this is a small series of cases, but the number of diabetics dying in hospital is not great; post-mortems are not carried out in every case, and only in a small proportion of these can permission be obtained to examine the eyes. It has, therefore, been thought advisable to issue a preliminary report setting out our findings to date.

METHODS AND TECHNIQUE

The post-mortem material from 21 diabetics was subjected to the following investigations:—

EYES: In two cases the posterior half of the eye was removed through the orbital roof; in all other cases one or both eyes were removed *in toto*. Where the whole eye was obtained it was fixed in 10 per cent. formal saline, frozen, cut transversely through the ora serrata and the frozen vitreous removed with forceps. It was realised early in the investigation that it is unsatisfactory to remove the posterior half of the eye at post-mortem. Retraction of the retinal vessels gives rise to the formation of loops which superficially resemble aneurysms (Fig. 1 and 2): great care must be taken in interpreting the appearances of such a specimen. The eye should always be removed completely and fixed in formal saline before opening.

Retina: The posterior attachment of the retina was severed by gently twisting a small capillary tube, the size of the disc, around the nerve from the inside. The retina was then floated out of the globe in saline and mounted in a glass sphere of the same shape and size. The specimen was thus examined macroscopically and in the slit-lamp; it was subsequently photographed in the sphere to record the severity of the retinopathy and the site of the micro-aneurysms (Fig. 3). The retinae were then removed and studied in a variety of ways:—

(*a*) Flat retina stained with the per-iodic method of Hotchkiss and McManus (1948, 1946) as applied by Friedenwald (1948) (Fig. 4) and the acetic-carbol-sudan method of Jackson (1944).

(*b*) Flat retina stained by the following method, devised in this laboratory, to demonstrate the blood content of the vessels.

70 per cent. alcohol. 5 minutes.
Saturated solution of benzidene in absolute alcohol. 5 minutes.
Ozonic ether—until the blue colour is well developed.
Xylol until clear and until bubbles have ceased to evolve (usually about 15-30 minutes).
Mount flat in canada balsam.

(*c*) Horizontal and vertical serial sections of the retina were stained with haematoxylin and eosin, Hotchkiss-McManus technique, Kimmelstiel-Wilson's basement membrane stain and Wilder's silver stain.

(*d*) The unfixed retina was shaken up with saline until it disintegrated; the suspension was centrifuged and the deposit stained with the Hotchkiss-McManus method. By this means vessels could be examined separate from retinal tissue.

Iris. The pigment layer was removed by blunt dissection under saline and the specimen was laid flat and stained in bulk with the Hotchkiss-McManus method. Horizontal serial sections of the iris were also stained by this technique.

Ciliary body. In cases where diabetic retinopathy was found the ciliary body was examined by serial sections stained with the Hotchkiss-McManus method.

Choroid. The choroid was removed from the eye, bleached with chlorine gas and stained as above.

Conjunctiva. In some cases there was sufficient conjunctiva for examination and a biopsy of conjunctiva was taken from a patient with diabetic retinopathy during an operation for cataract. The membrane was laid flat and stained by the Hotchkiss-McManus method.

Viscera. The capsules of the kidney and liver, the pleura, pericardium, omentum, peritoneum and bladder wall were fixed in formal saline and examined flat, in bulk, stained by the Hotchkiss-McManus and benzidene techniques. Figs. 5, 6, 7 and 8 show the vessels stained by both methods.

Brain. The vessels of the brain were examined (*a*) by smears of the fresh brain tissue stained with the Hotchkiss-McManus technique and (*b*) by shaking the fresh brain tissue in saline until the tissue was completely disintegrated; the suspension was then poured into a flat dish and the minute vessels were picked out with forceps and examined unstained and stained with methylene blue (Fig. 9) and the Hotchkiss-McManus method.

Paraffin sections were cut of the liver, kidney, heart, brain, lung and pancreas and they were stained with haematoxylin and eosin. Further sections were stained with the Hotchkiss-McManus technique, Kimmelstiel-Wilson's basement membrane stain and Wilder's silver stain. Frozen sections of the kidney were stained with Acetic-Carbol-Sudan (Jackson).

For the staining of paraffin sections of the kidney we found Friedenwald's modification of the Hotchkiss-McManus technique unsatisfactory. The following modification was evolved in the department and excellent results were obtained:—

SOLUTIONS.

Periodic Acid Soln. A. (Hotchkiss)	... ...	400 mg. periodic acid. 10 ml. distilled water. 5 ml. M/5 sodium acetate solution.

Immediately before use mix 15 ml. of this solution with 35 ml. ethyl alcohol.

Reducing Rinse (Hotchkiss) ... ... 1 g. potassium iodide.
1 g. sodium thiosulphate (pentahydrate).
20 ml. distilled water.
Add with stirring 30 ml. ethyl alcohol.
and then add 0·5 ml. 2 N HCl.
Leave for the deposit of sulphur to settle.

Fuchsin-sulphite Solution (Gradwohl, Vol. 11, page 2026). ... ... (A) 0·2 g. Basic fuchsin (as obtained from Gurr for Feulgen's reaction) dissolved in 120 ml. of hot distilled water. Cool.
(B) 2 g. sodium bisulphite in 20 cc. distilled water.

Add (A) to (B) then add to the whole 2 ml. concentrated hydrochloric acid, mix, and dilute the reagent to 200 ml. with distilled water.
Before use, leave overnight in the dark.
The solution should be a pale straw colour or colourless.

Saturated sulphurous acid (Carleton and Leach, page 63). ... ... To 200 ml. distilled water add
10 ml. 10 per cent. anhydrous sodium bisulphite soln.
and then 10 ml. N/1 HCl.

This solution should be made up fresh on the day of use.
Formalin fixed tissue. Paraffin sections 4 microns thick.
Bring sections to 70 per cent. spirit:

METHOD.

1. Alcoholic periodic acid. Solution A. 1 hour.
2. Rinse in 70 per cent. spirit.
3. Reducing rinse. 5 minutes.
4. Rinse in 70 per cent. spirit.
5. Fuchsin-sulphite solution. 1½ hours.
6. Saturated solution sulphurous acid 2 changes of 10 minutes each.
7. Wash in tap water 10 minutes.
8. Dehydrate quickly through spirit and alcohol. Clear in xylol and mount in canada balsam.

CONTROLS: Retinae were removed from all eyes coming to the department for routine examination and the retinae were examined flat after staining with the Hotchkiss-McManus method.

RESULTS AND DISCUSSION

To facilitate discussion our findings will be described under the questions we set out to answer.

1. *Are the vascular lesions in the retina true aneurysms (Ballantyne), simple capillary dilatations (Elwyn), nodular exudates or encysted haemorrhages?*

An aneurysm is usually defined as a localised arterial dilatation, formed by the vessel walls, within which blood circulates. Since these retinal lesions are largely confined to the venous side of the capillary network, the term is not strictly applicable to them; however, even if the name of capillary micro-aneurysm is accepted, it must still be decided whether these globular swellings on the vessels in diabetic retinopathy are vascular diverticula with walls

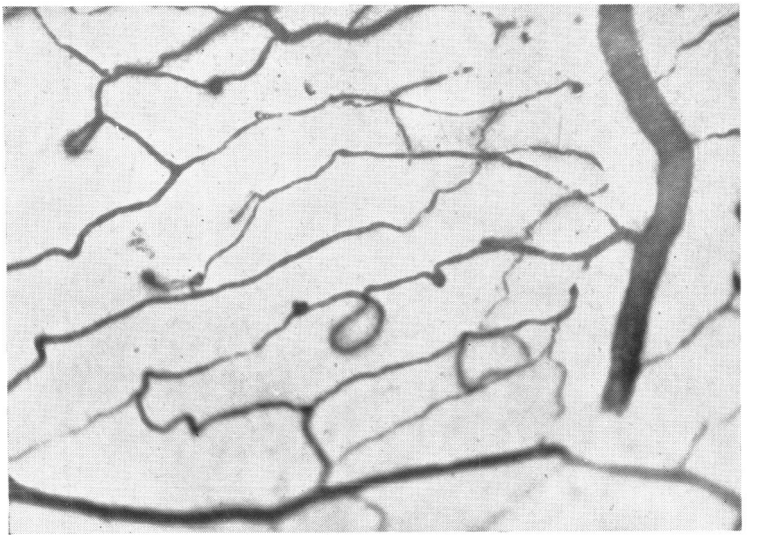

FIG. 1.

Case 8. Retina removed from the posterior half of the eye at post-mortem. The vessels have retracted to form loops which superficially resemble micro-aneurysms. Benzidene stain. × 66.

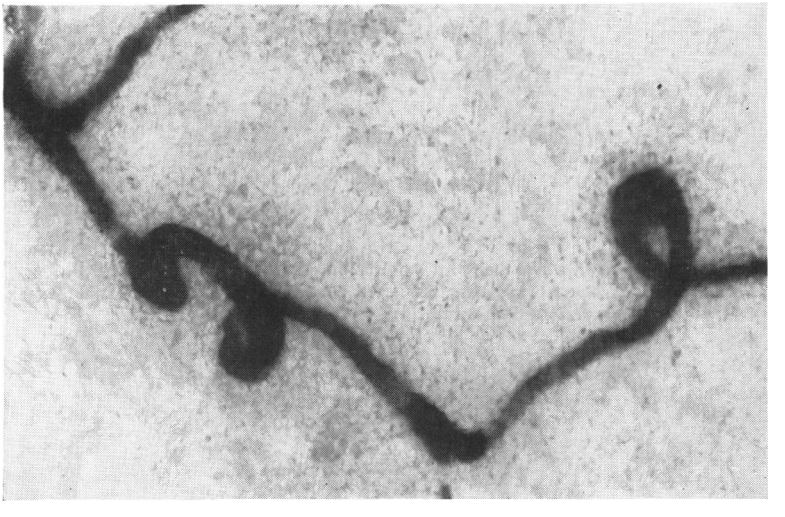

FIG. 2.

Case 8. High power view of Fig. 1. Shows looping of retinal vessels. Benzidene stain. × 950.

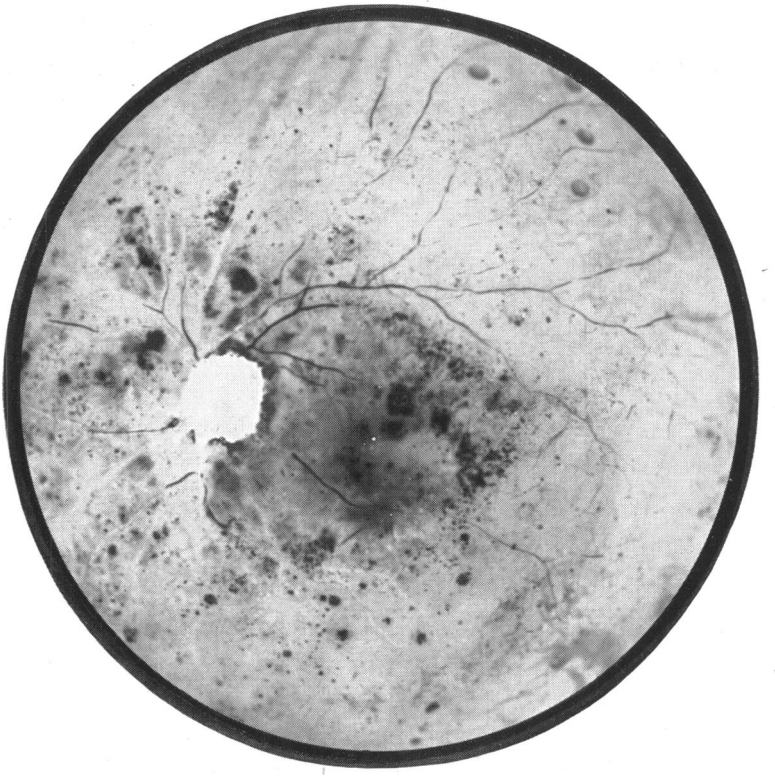

FIG. 3.

Case 14. Retina removed from the left eye and mounted in a glass sphere. Shows diabetic retinopathy stage III, with "dot and blot" haemorrhages scattered throughout the retina but particularly aggregated in the posterior polar region.

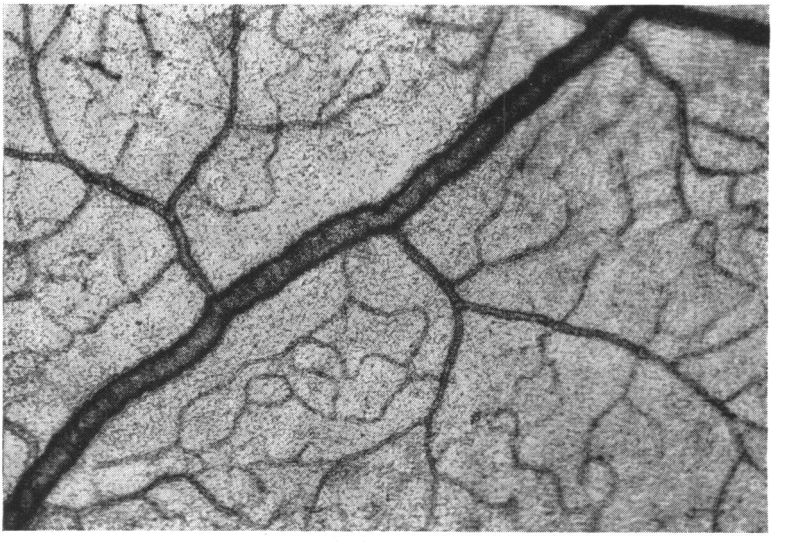

FIG. 4.

Normal retina showing the vessels stained by the Hotchkiss-McManus (Friedenwald) method. Flat preparation. × 66.

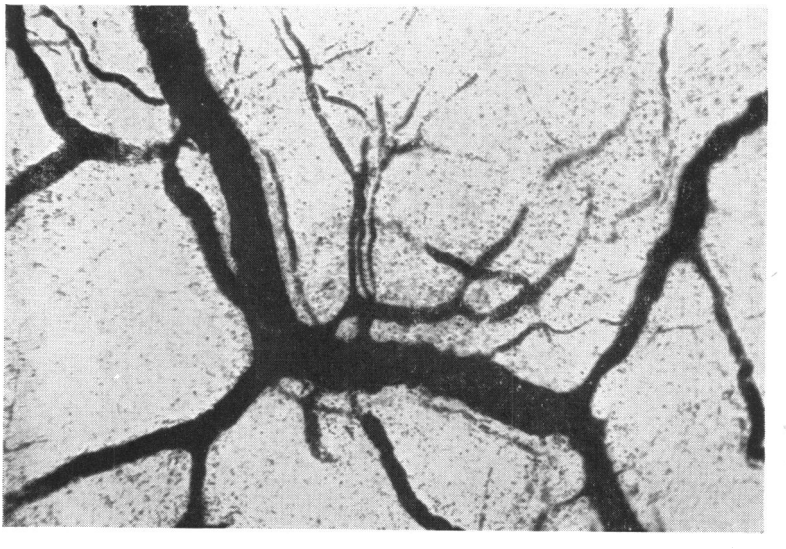

FIG. 5.

Meningeal vessels from a case with diabetic retinopathy. There is no evidence of aneurysm formation. Flat preparation. Benzidene stain. × 54.

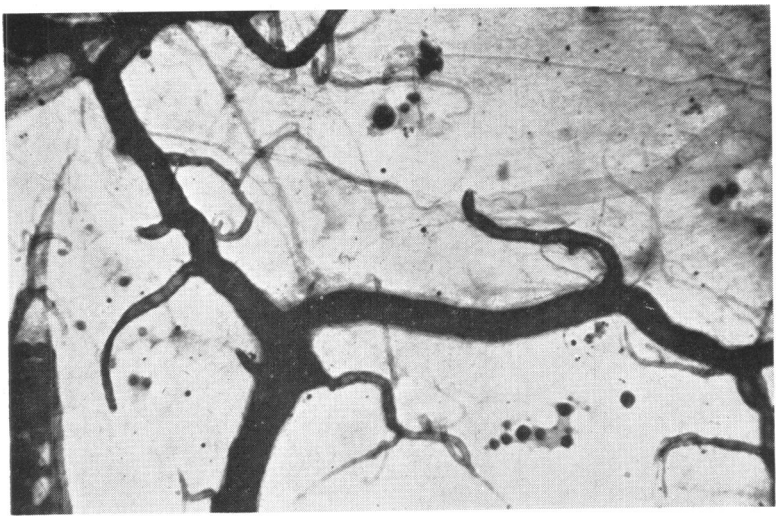

FIG. 6.

Meninges, from a case with diabetic retinopathy, stained by the Hotchkiss-McManus technique. The vessels and corpora amylacea stain an intense red. There was no evidence of aneurysm formation. × 42.

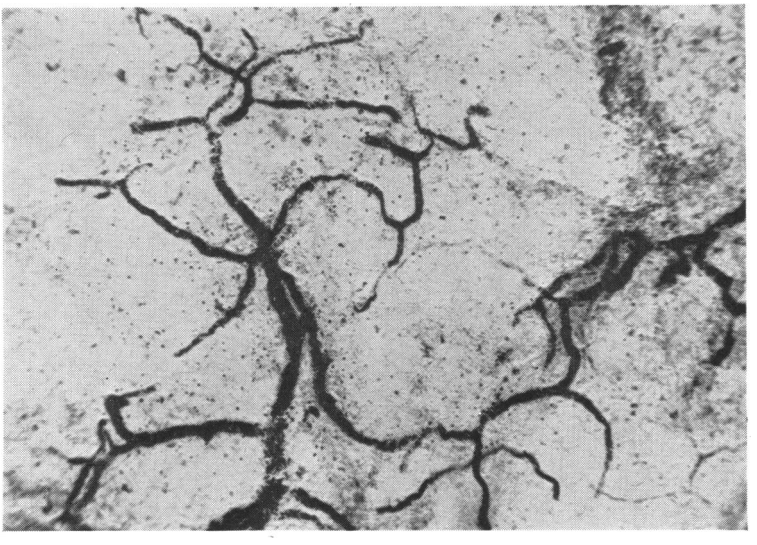

FIG. 7.

Pleural vessels from a case with diabetic retinopathy. There is no evidence of aneurysm formation. Flat preparation. Benzidene stain. × 60.

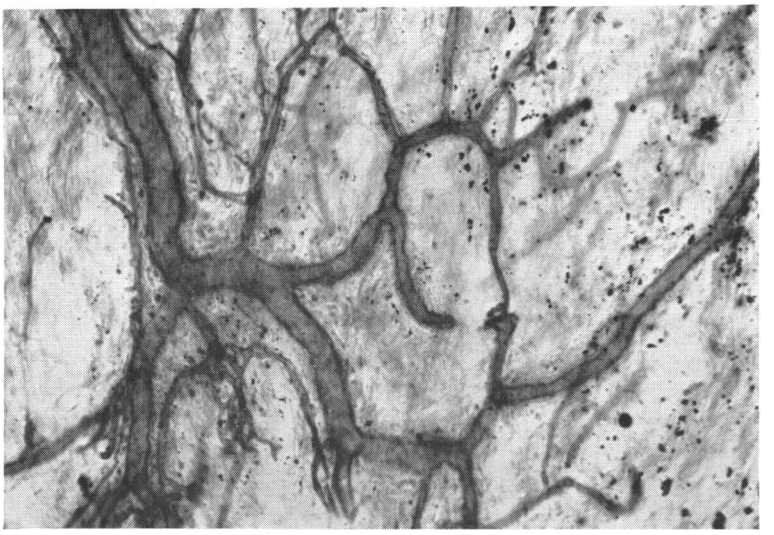

FIG. 8.

Pleural vessels from a case with diabetic retinopathy. There is no evidence of aneurysmal formation. The vessels show an intensely staining basement membrane. Hotchkiss-McManus stain. × 104.

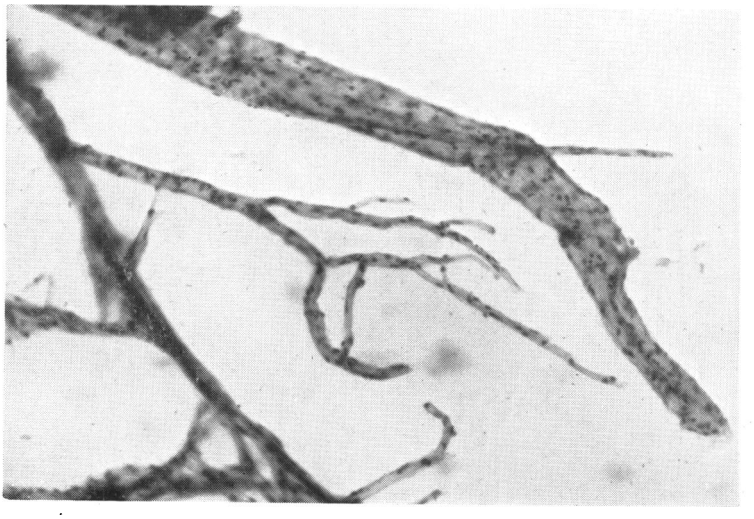

FIG. 9.

Case 15. Cerebral vessels from a case of diabetic retinopathy. There is no evidence of aneurysm formation. "Shake" preparation. Methylene blue. × 16.

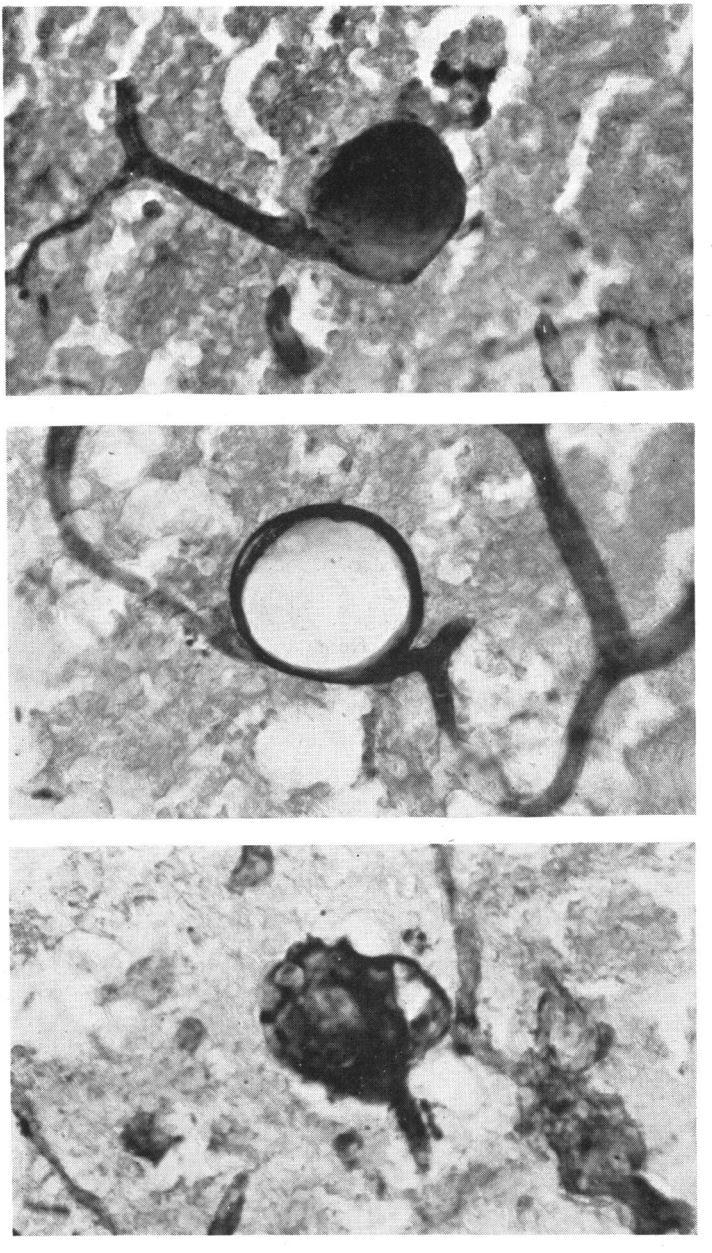

FIG. 10.

Case 14. Horizontal serial sections of the left retina. The upper section shows the inner wall of the aneurysm, the middle section passes through the centre and the lower section shows the outer wall. Hotchkiss-McManus (Friedenwald) stain. × 300.

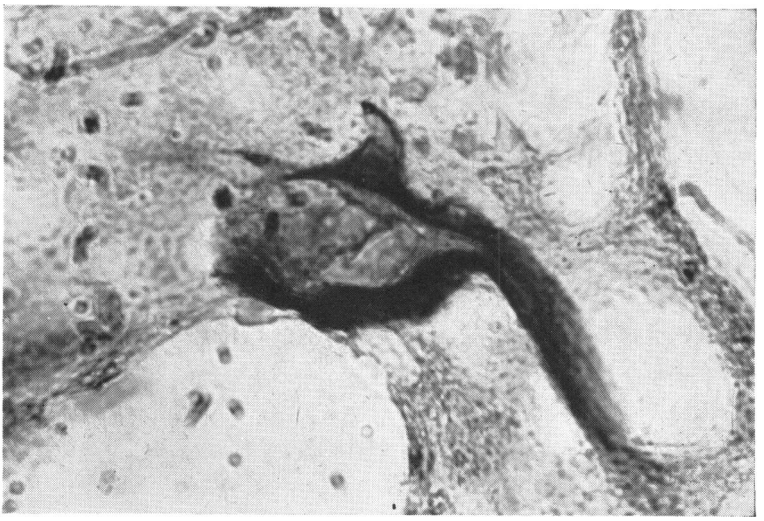

FIG. 11.

Case 21. Retinal capillary showing the vessel wall distending to form an aneurysm. Horizontal section of the retina. Hotchkiss-McManus (Friedenwald) stain. × 1066.

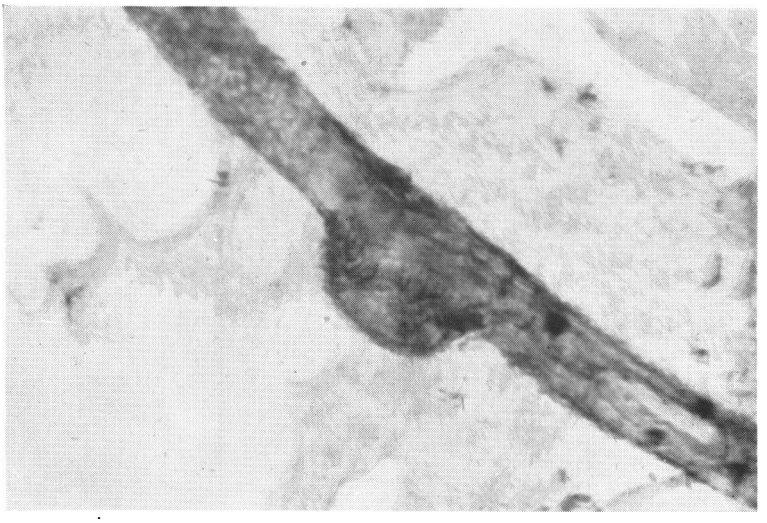

FIG. 12.

Case 21. Retinal capillary showing early micro-aneurysm formation. Horizontal section of the retina. Hotchkiss-McManus (Friedenwald) stain. × 932.

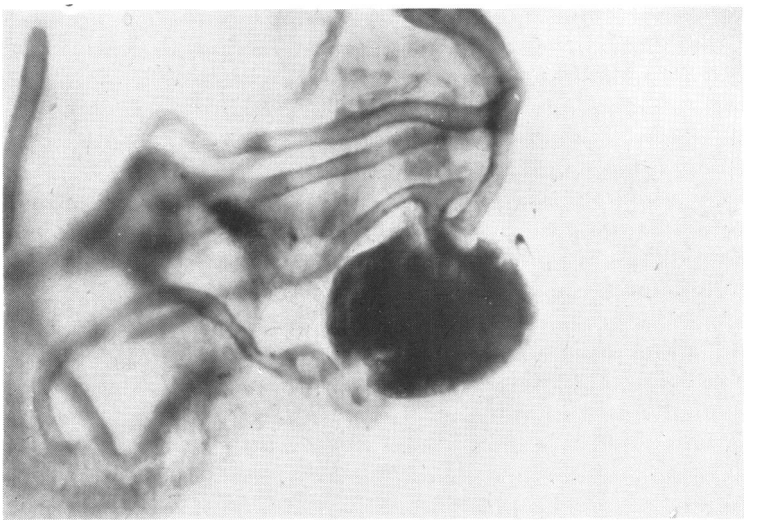

FIG. 13.

Case 15. Retinal vessels shaken free of retinal tissue. A well defined micro-aneurysm is present and the afferent and efferent vessel may be seen. Hotchkiss-McManus (Friedwald) stain. × 422. Diameter of aneurysm 77 microns.

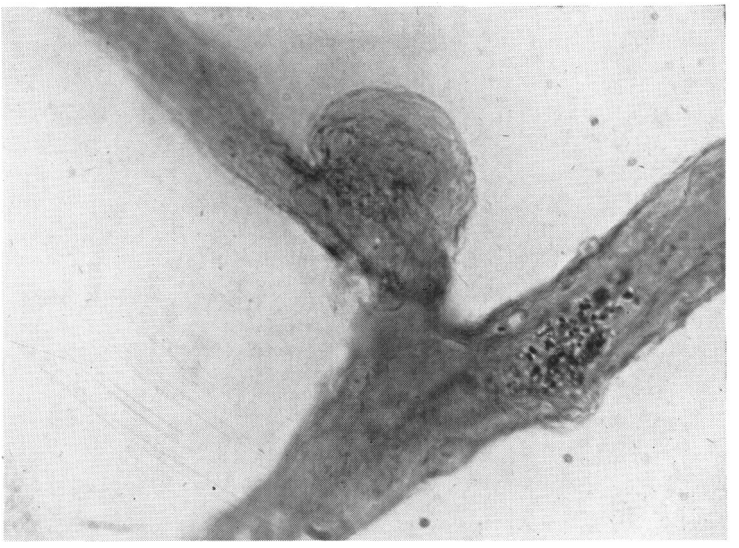

FIG. 14.

Case 15. Retinal vessel shaken free of retinal tissue. The intensely staining basement membrane can be seen extending into the wall of the aneurysm. Hotchkiss-McManus (Friedenwald) stain. × 684.

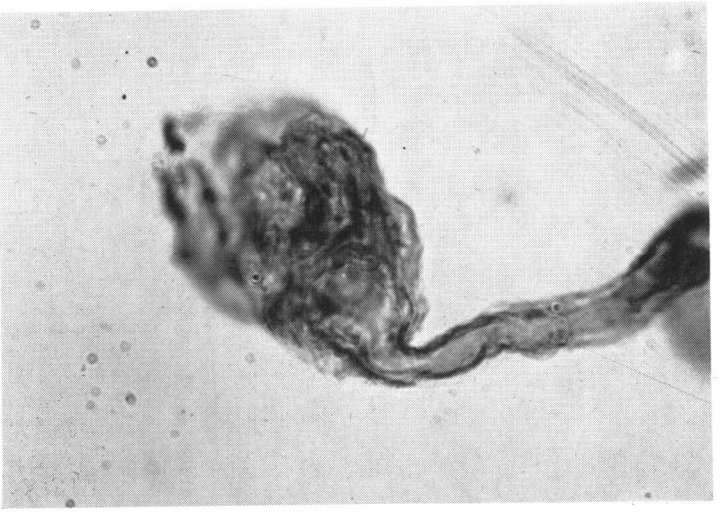

FIG. 15.

Case 15. Retinal micro-aneurysm shaken free of retinal tissue. There is degeneration and proliferation of the vessel wall: the basement membrane splits and disappears at the edge of the aneurysm. Hotchkiss-McManus (Friedenwald) stain. × 666.

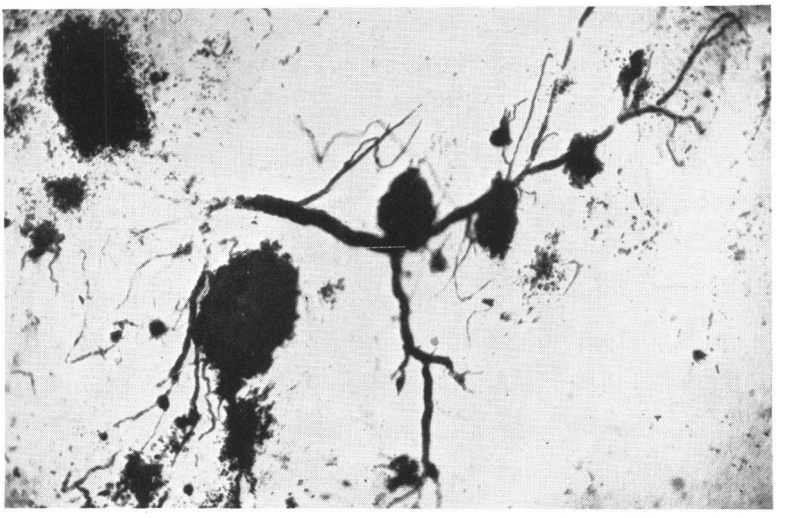

FIG. 16.

Diabetic retinopathy. Flat retina stained with benzidene showing irregular haemorrhages and micro-aneurysms containing blood. × 60.

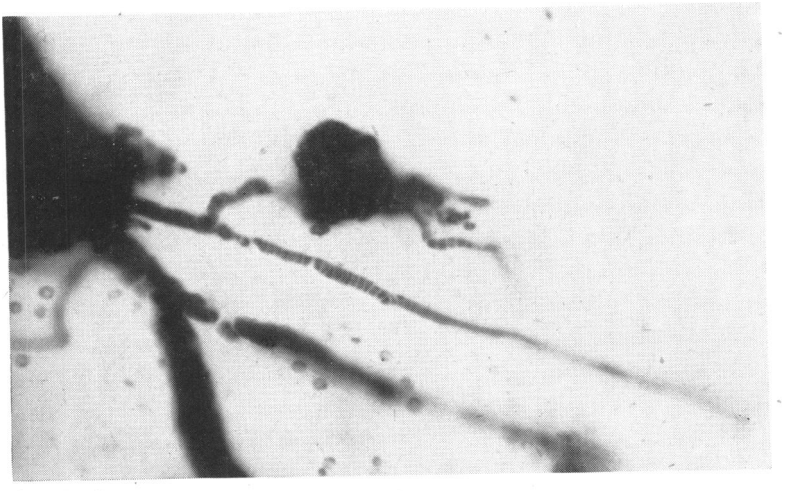

FIG. 17.

Diabetic retinopathy. High power view of Fig. 16. Shows a capillary micro-aneurysm containing blood. × 168.

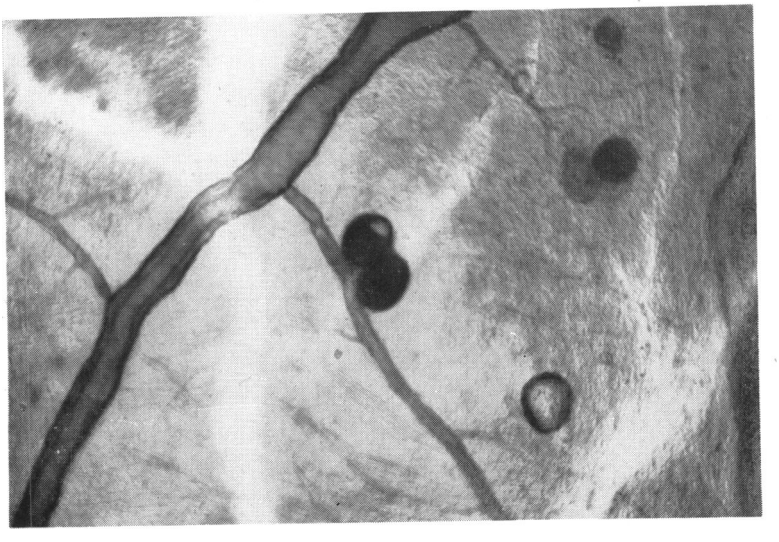

FIG. 18.

Case 14. Retinal micro-aneurysms. Left retina stained flat by Hotchkiss-McManus (Friedenwald) method. × 76.

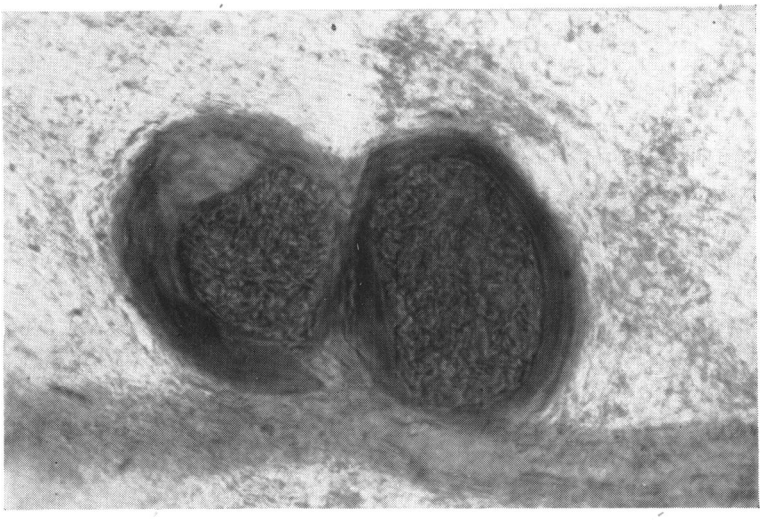

FIG. 19.

Case 14. High power view of two adjacent retinal micro-aneurysms seen also in Fig. 18. The lesions are remarkably localised and the remainder of the vessel appears normal. Hotchkiss-McManus (Friedenwald) stain. × 390.

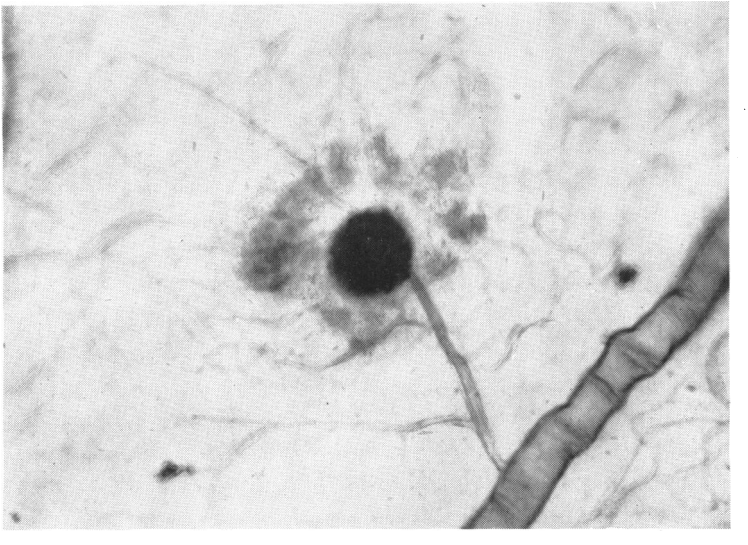

FIG. 20.

Case 14. Micro-aneurysm with surrounding haemorrhage. Left retina stained flat. Hotchkiss-McManus (Friedenwald) method. × 120.

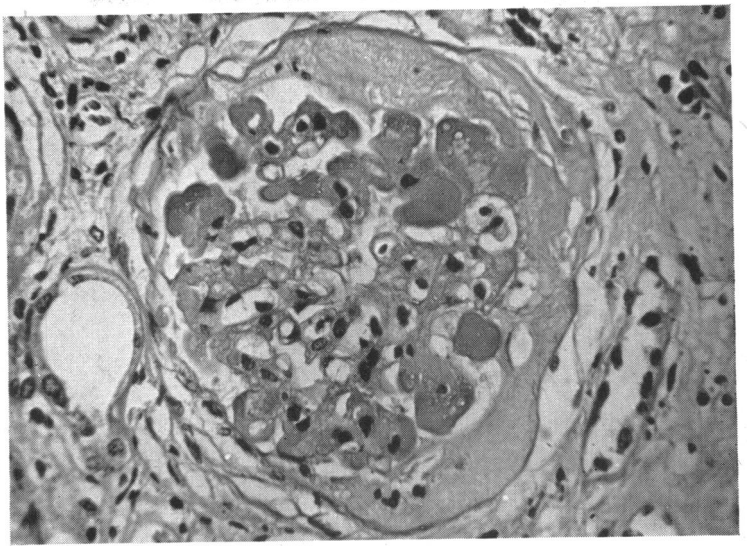

FIG. 21.

Case 15. Intercapillary glomerulosclerosis from a case with stage IV diabetic retinopathy. Note the club-shaped masses of hyaline material extending into the intercapillary connective tissue. H. and E. × 388.

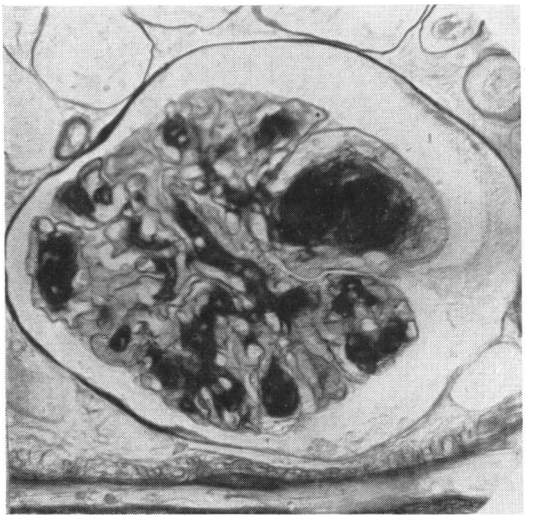

FIG. 22.

Case 24. Glomerulus showing intercapillary glomerulosclerosis. Hotchkiss-McManus stain (author's modification). × 250.

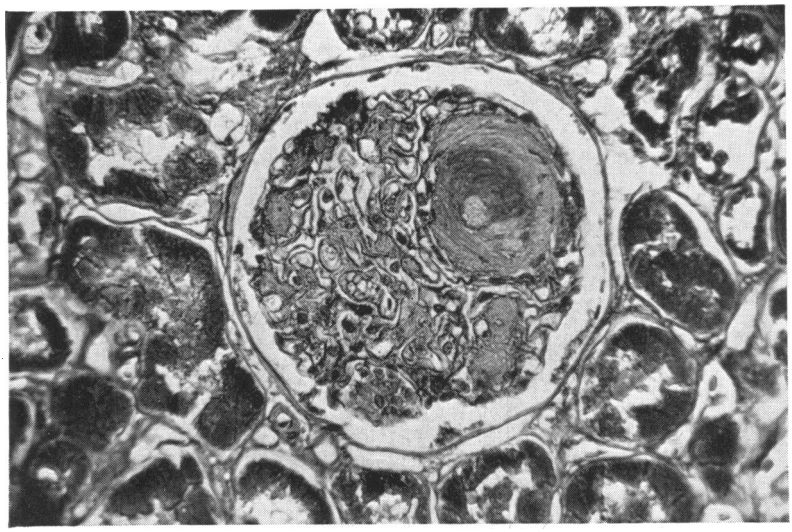

FIG. 23.

Case 24. Nodular type of intercapillary glomerulosclerosis showing lamination in the hyaline material. Paraffin section. Wilder's silver stain. × 254.

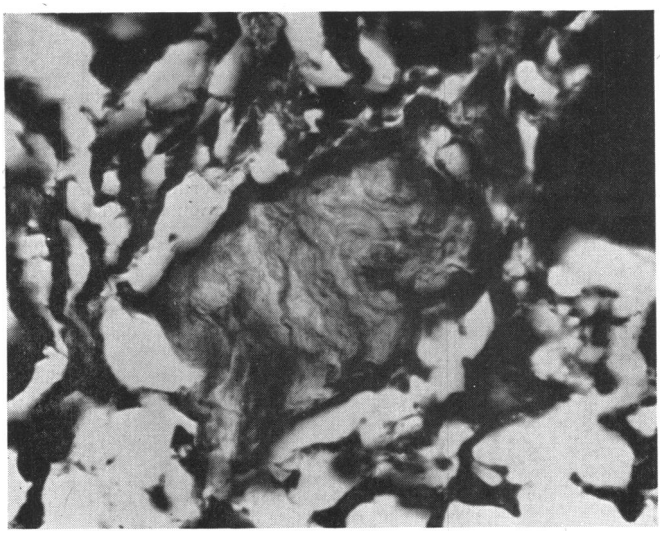

FIG. 24.

Case 15. Retinal exudate showing lamination. Compare with Fig. 23. Wilder's silver stain. × 660.

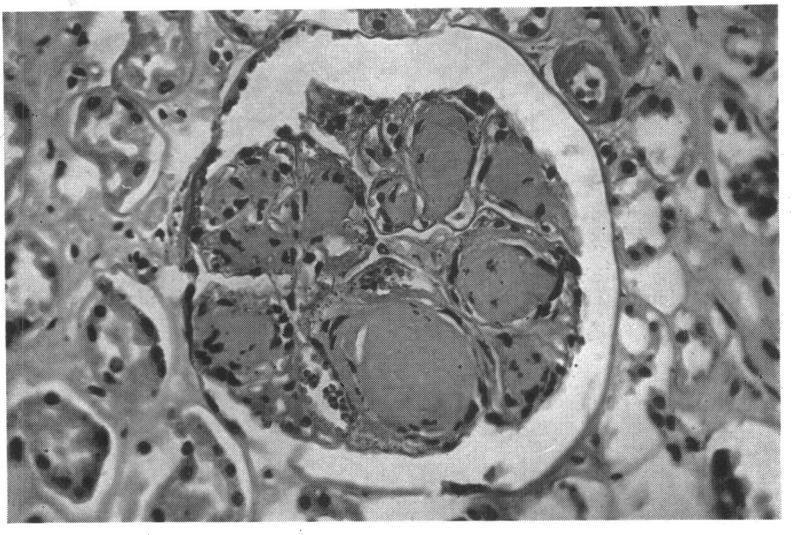

FIG. 25.

Case 24. Nodular type of intercapillary glomerulosclerosis showing localised dilatation of the vessels. Paraffin section H. and E. × 254.

formed by the coats of the vessels, or whether they are lesions unconnected with the vessel lumen. There is already considerable evidence that they are true aneurysms, for Ballantyne has shown that many of them at least are connected to a vessel, and his examinations of the flat retina have demonstrated blood within them. More recently, Friedenwald (1948) has applied the technique of Hotchkiss and McManus to the flat retina, and he has demonstrated the lesions in a most striking way. By this method polysaccharides are oxidised to polyaldehydes by periodic acid and the preparation is then stained with fuchsin-sulphite (Schiff's reagent); the exact details of the technique are given in Friedenwald's paper. Even better differentiation can be obtained if the rods and cones are first brushed off with a fine camel-hair brush. The vessel walls stain red and a more intensely staining basement membrane may be seen beneath the vascular endothelium. Friedenwald regarded the vascular nodules in diabetes as true aneurysms because they had an afferent and efferent connection; although this is a point in favour, it is not completely convincing, and we have sought to obtain an actual section of one of these lesions at the site of its vascular origin. This was eventually obtained in a series of horizontal sections of the retina, stained with the Hotchkiss-McManus method (Fig. 10), and it leaves little doubt that these vascular nodules are in fact true aneurysms. This is further supported by Fig. 11, which shows the vessel wall distending to form the aneurysm. Aneurysmal formation at an early stage is shown in Fig. 12. Figs. 13 and 14 are vessels floated out of the retina as described earlier; Fig. 13 clearly shows the afferent and efferent vessels, and Fig. 14 shows the basement membrane continuing into the aneurysmal wall; and Fig. 15 shows not only aneurysmal formation, but also degeneration and proliferation of the vessel wall. It will be seen that the basement membrane disappears suddenly at the edge of the aneurysm. That the aneurysms contain blood is clearly shown in the flat retina stained by the benzidene method (Figs. 16 and 17); this was further demonstrated in serial sections stained with haematoxylin and eosin. One of the most striking features of these lesions is that their point of origin may be extraordinarily localised. In most cases they arise from one side of the vessel only, while the opposite side appears perfectly normal, showing no signs of distension. The two aneurysms shown in Figs. 18 and 19 apparently arise from two adjacent foci, which must have been remarkably well circumscribed by healthy tissue for such a lesion to have resulted. Fusiform aneurysms are uncommon; the majority are saccular diverticula.

From this evidence we are, therefore, able to confirm Ballantyne's original contention that these lesions are true micro-aneurysms.

2. *Where are the aneurysms situated in the retina?*

It has long been known that the fundus haemorrhages in diabetes are at first confined to the macular and peri-macular area and that they take the form of " dots and blots." In the later stages they become larger and more widespread while more irregular haemorrhages then predominate. The Hotchkiss-McManus staining technique as modified by Friendwald demonstrates better than any previous method that the well defined " haemorrhages " are all micro-aneurysms and that the irregular haemorrhages are extravasations of blood usually related to an aneurysm which appear to arise either by diapedesis of the red cells through the aneurysmal wall (Fig. 20) or by actual rupture of the aneurysm. This has already been demonstrated by Ballantyne and Friedenwald. In this series of cases examination of the retina mounted in a glass sphere showed both types of lesions scattered throughout the fundus but particularly aggregated in the posterior polar region. The anterior nasal area appears to be the least affected; in one of our cases, however, micro-aneurysms were evenly scattered throughout the whole fundus. Microscopical examination confirmed Ballantyne's report that they are situated mainly in the inner nuclear layer in the course of the capillaries which link the deeper and more superficial capillary plexus of the retina.

3. *Do micro-aneurysms occur elsewhere in the eye when diabetic retinopathy is present?*

In all cases in which diabetic retinopathy was present the iris, ciliary body and choroid were removed for examination by the methods previously described. After a prolonged search no definite micro-aneurysms were found in any of the preparations. No micro-aneurysms were found in the conjunctiva removed at post-mortem or in the biopsy specimen. From this small series of cases it is, therefore, legitimate to conclude that micro-aneurysms probably do not occur in the eye apart from the retina.

4. *Do micro-aneurysms occur elsewhere in the body when diabetic retinopathy is present?*

Examination of the cerebral vessels and of flat preparations of the omentum, peritoneum, pleura, pericardium, meninges, bladder wall, liver and renal capsules showed no evidence of micro-aneurysmal formation in any case, irrespective of whether

retinopathy was present or not. Serial paraffin sections of the organs removed at autopsy have not yet been studied but judging from the evidence so far obtained it would appear that micro-aneurysms do not occur in the vessels of the brain or serous membranes.

5. *What gives rise to micro-aneurysms and why are they confined to the retina?*

In attempting to explain the formation of micro-aneurysms in diabetic retinopathy, Ballantyne (1945) has suggested that they may result from the injurious effects of an unknown circulating chemical toxin, which is highly selective for the retinal capillaries. That such specific toxins exist is well known; Ballantyne draws an analogy with alloxan (mesoxalyl urea), which when administered to experimental animals destroys only the pancreatic islets (Dunn *et al*, 1943). The presence, however, of intercapillary glomerulosclerosis and other vascular lesions in diabetes, together with the frequently reported increase in capillary fragility, as measured by compression of the arm, indicate that the vascular disease is much more widespread and it would seem probable that the formation of aneurysms in the retina is simply an expression of this vascular degeneration brought about by mechanical factors peculiar, either to the retinal vessels themselves or to their immediate environment. Clinicians have often commented upon the engorgement of the retinal veins in diabetes and Michaelson and Campbell (1940), in a study of the anatomy of the finer retinal vessels, have pointed out that the deep plexus of vessels is a more closely-knit meshwork than the superficial one and that venous stasis is consequently most felt in these capillaries: it is in the deep plexus that the majority of micro-aneurysms occur. In other words it would appear that aneurysm formation is related to venous stasis and the peculiar structure of the retinal capillary network. The cause of the venous stasis is unknown. Hyperglycaemia of long duration is the important factor according to Elwyn, but Cristini and Tolomelli (1947) affirm that in the diabetic subject with retinitis there is frequently sclerosis of the larger pre-capillaries in the retina which brings about a condition of stasis with a resulting decrease of retinal arterial pressure and an increase of retinal venous pressure. The correct explanation, however, remains obscure.

Weinstein (1948) has suggested that haemorrhages in the diabetic fundus occur when dilatation of the retinal capillaries is associated with low ocular tension. It may be possible, therefore, that variations in ocular tension resulting from fluctuation in the blood sugar level may also be a factor in the formation of micro-aneurysms.

6. *What is the relationship of Kimmelsteil-Wilson's intercapillary glomerulosclerosis to diabetic retinopathy?*

In order to relate these two conditions it was first necessary to classify them in stages of severity. In deciding upon the presence or absence of intercapillary glomerulosclerosis, mild diffuse intercapillary thickening was neglected and only those sections showing definite globular or club-shaped masses of "hyaline" material in the glomerular tuft were considered positive and they were categorised as mild, moderate and severe according to the observer's impression of the degree and extent of the pathological change (Figs. 21 and 22).

The existing classifications of diabetic retinopathy refer to ophthalmoscopical appearances but minute aneurysms could be seen in the microscopical examination of the retina when the fundus appearances in life were normal. For the purpose of this investigation, therefore, the following grouping based upon Ballantyne's (1946) clinical classification was adopted:—

I. *Subclinical stage.* Where micro-aneurysms were found only on microscopical examination of the stained retina.

II. *Mild stage.* Changes chiefly in the central area; micro-aneurysms with or without punctate exudates.

III. *Moderate stage.* Dot and blot haemorrhages with confluent waxy exudates.

TABLE I

Case No.	Age	Sex	Known duration of diabetes in years	Retinopathy	K.W. disease	B.P. Systolic
1	52	M	25	0	0	150
3	72	M	4	0	0	160
5	59	F	—	0	0	190
7	75	M	35	I	0	170
8	12	F	1	0	0	—
9	63	F	13	II	Mild	85
10	67	M	14	I	0	—
11	73	F	—	0	0	100
12	75	F	—	I	0	160
13	68	F	—	0	0	—
14	73	F	5	III	Moderate	175
15	57	M	10	IV	Severe	210
16	60	F	3	I	Moderate	210
17	75	F	—	0	0	220
18	70	F	—	0	0	—
19	63	M	—	III	Mild	190
20	79	F	13	II	0	200
21	79	F	—	II	Severe	180
22	47	M	2 weeks	0	0	160
23	52	M	10	I	0	—
24	86	F	1 month	II	Severe	200

IV. *Severe stage.* Massive exudates and extensive retinal haemorrhages. Retinitis proliferans, detachment of the retina and vitreous haemorrhages.

As will be seen in Table I, retinopathy, as defined above, was present in 12 (57.12 per cent.) of the 21 cases examined and of these 7 (58.3 per cent.) showed Kimmelstiel-Wilson's disease of the kidney. The renal lesion was not found in any case where the retinal vessels were normal; the intercapillary glomerulosclerosis was always accompanied by retinal micro-aneurysms. Of the 5 cases of diabetic retinopathy in which the glomeruli were normal, 4 were subclinical and 1 was mild. The 3 more advanced forms of retinopathy were each associated with intercapillary glomerulosclerosis. This is too small a series of cases from which to draw conclusions of any great value but the implications appear to be that intercapillary glomerulosclerosis in the diabetic is regularly associated with retinal micro-aneurysms, whether they are detectable ophthalmoscopically or not, and that while retinopathy in the early stages may or may not be associated with the renal complication, the severe form is probably always associated with intercapillary glomerulosclerosis, but, when the two lesions co-exist, there is no correlation between their degrees of severity. These findings, as far as they go, are in accord with the report of Henderson *et al.* that advanced retinopathy is more or less regularly associated wth intercapillary glomerulosclerosis. Kimmelstiel and Porter found retinopathy in 86 per cent. of cases with the advanced renal lesion, but this percentage was based upon ophthalmoscopical appearances; it is probable that if it had been possible to examine the retinae microscopically a much higher figure would have been obtained. As stated above, microscopical or ophthalmoscopical retinopathy was present in 100 per cent. of our cases with intercapillary glomerulosclerosis, irrespective of the degree of severity of the glomerular involvement. It will be interesting to see whether this incidence is maintained in a larger series.

The problem of the aetiological relationship of the retinal and renal lesions is a less simple one, but after studying sections of intercapillary glomerulosclerosis and diabetic retinopathy side by side, it is difficult to resist the conclusion that one is dealing with manifestations of exactly the same pathological process modified by the different anatomical structures. In both there is localised capillary dilatation; in both there is localised degeneration and proliferation of the vessel wall. In one there is the formation of " hyalin " and in the other of " waxy exudates "; the chemical structure of neither is known and they may well be closely related. Allen's (1941) detailed studies of the glomerular lesion included

an attempt to assign definitive characteristics to the generic term " hyalin " by tryptic digestion and special staining; in the diabetic lesion he found resistance to tryptic digestion, affinity for aniline blue and marked argyophilia and lamination with silver stain. To this can be added the fact that this " hyalin " stains red with the Hotchkiss-McManus method. Apart from tryptic digestion, which we have not yet tried, all the above reactions may be demonstrated in the diabetic " waxy exudates " (Figs. 23 and 24). Frozen sections of the kidney and retina stained with acetic-carbol-sudan show that both the " hyalin " and " exudate " are intimately mixed with fat globules. Widespread difference of opinion exists among pathologists as to the exact site of the deposition of " hyalin " in the glomerulus; Kimmelstiel and Wilson claim that it is in the intercapillary connective tissue and Allen states that it is intramural. If we assume that there is, in fact, a close relationship between the retinal and renal lesions, a study of the retinal vessels in diabetes may throw some light on the problem. In the retina the vessels show a degeneration and proliferation of the vessel wall itself (Fig. 15) with the passage of " exudates " into the surrounding tissue. By analogy, therefore, it would seem possible that the hyalin in Kimmelstiel-Wilson's disease may be both intramural and intercapillary. Friedenwald suspects that the capillary dilatations associated with intercapillary glomerulosclerosis (Fig. 25) are also micro-aneurysms and on these grounds he brings the lesion into line with the retinopathy. Even if this were true, the presence of hyaline masses compressing the capillaries in the glomerulus, within the confines of Bowman's capsule, offers a purely mechanical explanation for the presence of localised capillary dilatations, which cannot apply in the retina, and it is doubtful whether the similarity of the lesions is more than superficial. Apart from this point, however, we are in complete agreement with Friedenwald's suggestion that both intercapillary glomerulosclerosis and diabetic retinopathy are manifestations of the same vascular process.

Redslob (1948) believes that it is impossible to distinguish ophthalmoscopically between diabetic and nephritic retinal lesions; the only difference he recognises is the absence of oedema in diabetic retinopathy and in his view, the two are analagous if not identical. Redslob feels that the answer to the problem of diabetic retinopathy is to be found in intercapillary glomerulosclerosis and he thinks it extremely probable that the renal lesion gives rise to the retinopathy. Our findings do not support this theory. A reference to Table I shows that no less than 5 of our cases had retinopathy without any evidence of glomerular involvement and this finding together with the fact that the more severe form

of retinopathy is regularly associated with intercapillary glomerulosclerosis suggests rather the reverse of Redslob's argument, *i.e.*, that the retinal disease precedes the renal lesion. That the development of intercapillary glomerulosclerosis may aggravate the retinopathy cannot be denied, however.

Thus the aetiology of both the renal and retinal lesions remains obscure and the elucidation of their exact relationship must await the solution of the larger problem of the cause and nature of the widespread vascular degeneration in the diabetic.

SUMMARY

Accumulated experience in pathological and clinical studies during the last few years points to a particular type of vascular degeneration in diabetes which is responsible for at least some of the more important complications of this disease. The evidence in the literature for this conclusion is briefly reviewed.

An investigation is being undertaken to compare the histopathological changes in the diabetic retina with disease in the vascular system generally and a preliminary report is given upon the examination of post-mortem material, including the eyes, from 21 diabetic patients.

The vessels of the retina, choroid, ciliary body, iris, conjunctiva, brain, meninges, pleura, pericardium, omentum, peritoneum, bladder mucosa and the capsules of the kidney and liver were examined by new methods of staining and preparation.

Ballantyne's report that the globular lesions on the retinal vessels are true capillary micro-aneurysms is confirmed and the methods employed have demonstrated further features in their morphology.

Micro-aneurysms were not found outside the retina, either in the eye, in the cerebral vessels or in the vessels of serous membranes, bladder wall or omentum. Their mode of origin is discussed and explanations for their localisation in the retina are advanced.

In each case the kidneys were examined for Kimmelstiel-Wilson's disease and the lesion was related and compared to the retinopathy. It is believed that intercapillary glomerulosclerosis and retinopathy are manifestations of the same pathological process modified by the different anatomical structure of the retinal and glomerular vessels.

The findings are not in accord with Redslob's belief that intercapillary glomerulosclerosis causes diabetic retinopathy. Early retinopathy can exist in the absence of intercapillary glomerulosclerosis and our investigation suggests that retinal changes probably precede the deposition of hyaline material in the glomerulus.

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