RETINAL MICRO-ANEURYSMS IN CONNECTION WITH GENERALIZED DISEASES CAUSING RETINOPATHY*

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ARTERIOSCLEROSIS, nephrosclerosis, nephritis, and diabetes give rise to clinical pictures in the retina which may so closely resemble each other that it is sometimes impossible to differentiate between them ophthalmoscopically. The aetiology of these retinal diseases has been the subject of much study and the numerous theories have recently been reviewed by Ayoub (1950). Among the oldest is that of von Graefe and Schweigger (1863) who believed that renal retino-pathy is simply part of the general disease of the vascular system. Duke-Elder (1940) states that most pathologists would prefer to assume the presence of two factors:

(1) hypertension with ischaemia and subsequent malnutrition,

(2) the effect of some toxin or toxins unknown.

The existence of a toxin causing hypertension (renin) was established by Tigerstedt and Bergman (1898).

Especial attention has been given in recent years to diabetic retinopathy. Franceschetti and Streiff (1939), Hanum (1938), Ballantyne (1946), Radnót (1948), Appel (1950), Mårtensson and Palm (1950), and others, declare that hypertension, although a frequent accompaniment of diabetic retinopathy, is not an essential factor in its aetiology. Ballantyne (1946) and Gartner (1950), among others, point out the inefficacy of insulin in the treatment of retinopathy.

Retinopathy is attributed by Smith (1950) to capillary dilatation, and by Pines (1950) to a toxin affecting mainly the capillaries and the venous system.

Interest was aroused in the retinal changes caused by diabetes when Ballantyne and Loewenstein (1944) demonstrated the existence of micro-aneurysms by new techniques they had developed. A number of ophthalmologists studied these formations in the retinal capillaries. Ballantyne (1945) noted their occurrence as primary signs of diabetes, Friedenwald (1949, 1950) found the aneurysms very

* Received for publication April 6, 1951.
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frequently in diabetic patients but rarely in other diseases. Ashton (1949) established the formations as true aneurysms and studied the problem more widely in other respects. Day (1950) rarely found them apart from diabetes; he sometimes noted an isolated aneurysm in hypertension. Becker and Post (1950) saw them in association with stasis in the central vein. Ashton (1950) searched for aneurysms in other tissues of the eye and in other organs; apart from their probable existence in the glomerulus affected with Kimmelstiel-Wilson’s disease (Kimmelstiel and Wilson, 1936), he found them confined to the retina, none being revealed even in the serous membranes of the body. Day (1950) and Friedenwald (1950), on the other hand, saw aneurysms in the capillaries of the fingernail folds of diabetics; McCulloch and Pashby (1950) discovered aneurysms in the conjunctivae of diabetic patients and considered them as part of the disease process, but Vogt (1941) found them relatively frequently in the conjunctivae of elderly people.

Micro-aneurysms have, therefore, been found occasionally in diseases other than diabetes, but no systematic research on the subject has yet been reported. The present paper attempts to throw light on the question of the incidence of aneurysms in other general diseases which, like diabetes, are associated with retinopathy.

METHODS AND MATERIAL

One hundred and forty-three pairs of eyes, taken from paraffin wax blocks, were studied. The condition of the material made it impossible to use the injection techniques of either Ashton (1950) or Michaelson and Steedman (1949). The retinæ were removed from the eyes and stained by the method of Hotchkiss (1948) and McManus (1946, 1948), as described by Friedenwald (1949). In some cases, by means of section preparations, the retinal lesions were shown to be true aneurysms. The retinæ flattened on the glass slides were detached again and placed in paraffin wax according to the simplified technique of von Fieanıt and Saxén (1932, 1936):

A glass cylinder is glued onto a glass slide, thus forming an embedding cup, into the bottom of which the retina is pressed flat with a pad. It is kept in this position and embedded in wax; the glass slide may then be detached and the block pressed out from the cylinder.

The retina is now flat on the surface of the block and may quite easily be cut into thin sections parallel with the surface.

Since the series contained only a few diabetic retinæ, and in view of the fact that much work has already been done upon this subject, I shall not discuss this disease in connection with my own series.

The classification into arteriosclerosis, nephrosclerosis, and nephritis, was made on the basis of the clinical picture and post-mortem findings. Complete autopsy was carried out in each of the cases. A control series of patients, in which there was no evidence either clinically or at autopsy, was introduced for comparison (see Table).

RESULTS

It should first be noted that, in the series, aneurysms occurred in patients with arteriosclerosis, nephrosclerosis, and nephritis. The incidence of micro-aneurysms in these cases will be discussed later.
Fig. 1.—Numerous retinal micro-aneurysms in a 60-year-old arteriosclerotic patient. No nephrosclerosis revealed at autopsy. ×72.

Fig. 2.—Retinal micro-aneurysms in a 59-year-old nephrosclerotic patient. In the circle a varicose vascular dilatation may be seen adjacent to a spherical aneurysm. ×72. (Cf. Fig. 4.)

Fig. 3.—Spherical retinal aneurysms in a 65-year-old nephrosclerotic patient. ×360.

Fig. 4.—Spherical and elongated varicose capillary aneurysms in the retina of a 59-year-old nephrosclerotic patient. ×360.

Fig. 1 shows a number of micro-aneurysms of different sizes in a case with established generalized arteriosclerosis but no renal lesion. The aneurysms in Figs 2 and 3 are from nephrosclerotic patients. Fig. 4 shows the same lesions as Fig. 2 in higher magnification and Fig. 7 shows them in section. Retinal micro-aneurysms from a patient with nephritis are seen in Figs 5 and 6, the same lesions being shown in section in Fig. 8.

Two main types of aneurysms were noted: a localized spherical type (Figs 1, 2, and 3), and an elongated, fusiform, varicose type (Figs 2, 4, and 7). There is no discernible difference between the
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Fig. 5.—Retinal micro-aneurysms in a 24-year-old nephritic patient. Higher magnification of the area inside the circle is shown in Fig. 6. ×72.

Fig. 6.—Higher magnification of the area within the circle in Fig. 5. Aneurysms occur at points of capillary bifurcation and also between them. ×360.

Fig. 7.—Retinal micro-aneurysms in section, from a 59-year-old nephrosclerotic patient. ×360.

Fig. 8.—Retinal micro-aneurysms in section, from a 24-year-old nephritic patient. ×360.

aneurysms occurring in the different diseases. They occur both at the points of vascular bifurcation and between them.

The case of a 24-year-old patient with renal disease, who exhibited a large number of micro-aneurysms in the retinal vessels, is seen in Figs 5, 6, and 8. Generalized arteriosclerosis would be most improbable at this age and, in fact, neither the autopsy nor sections made from different parts of the eye revealed evidence of arteriosclerosis; nor were there any clinical or post-mortem findings to suggest diabetes.

As the Table (overleaf) shows, no aneurysms were found in the control material (51 cases), but they occurred in all the other
TABLE
CONTROLS AND PATIENTS, BY AGE GROUPS

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groups and their frequency varied with the age of the patient. For the separate diseases there was a similar frequency, just below 40 per cent., but no exact incidence can be established from such a small series. Friedenwald (1950) found 43 cases with aneurysms among 76 diabetic patients studied: the frequency would thus be somewhat greater in diabetic patients (about 55 per cent.), but here again the material is too small for any accurate calculation of the percentage. It is clear, however, that there is a similar frequency of aneurysms in patients with arteriosclerosis, nephrosclerosis, nephritis, and diabetes, although diabetic patients seem to have them more often than the rest.

In the present material, generalized arteriosclerosis occurred only over the age of 41 years. In a previous study (Sysi, 1949), arteriosclerosis was seen earlier in patients with nephritis, in the age group 31–40. Nephrosclerosis, on the other hand, was very rare in patients under 51 (only two cases), but the number of cases increased rapidly after that age. Cases of nephritis were evenly distributed between 16 and 80 years of age.

In comparing the frequency of aneurysms in the different disease groups, they were noted more frequently in cases with arteriosclerosis in the younger age groups and their incidence diminished with advancing age. In the younger age groups of patients with generalized arteriosclerosis, aneurysms were found more commonly than in the corresponding nephrosclerotic group, in which aneurysms appeared
at a greater age and were fairly equally distributed in different age groups. In the oldest age group the frequency of aneurysms is thus greater for nephrosclerotic than for arteriosclerotic cases.

In the group of nephritic patients an approximately equal number of aneurysms was noted in the different age groups.

DISCUSSION

The above findings, together with some views expressed in the literature, induce me to bring forward some theories as regards the diseases with which we are dealing at present.

Ballantyne (1945) noted that aneurysms may be the earliest retinal sign of diabetes. According to Ashton (1949), diabetic changes in the retina often precede the intercapillary glomerulosclerosis of Kimmelstiel and Wilson (1936). We found a greater incidence of aneurysms in arteriosclerotic patients of the younger age groups than in those of the older age groups, and the reverse relationship in patients with nephrosclerosis, which may be taken to imply that the aneurysms of arteriosclerotic patients indicate a development of the disease into nephrosclerosis. This theory, which cannot be proved within the scope of the present material, will be studied further by subjecting the retina to microscopy with a slit lamp, in vivo.

The retinal changes are caused by or associated with three diseases which sometimes closely resemble each other. The three diseases, namely, nephritis, arteriosclerotic contracted kidney, and diabetes, are also accompanied by other common or closely related signs, such as vascular changes, hypertension and renal disease (nephrosclerosis and intercapillary glomerulosclerosis). Recent research, Rintelen (1939) and Sysi (1949), for example, has disproved earlier views that vascular changes in the retina necessarily imply disease in the vessels of the brain, although it has confirmed the theory that renal and retinal vascular changes are closely inter-related.

The old view that diabetic and renal retinopathy originate from renal disease was last put forward by Redslob (1948), who considers the two retinopathies identical or analogous. Ashton (1949) disagrees with this view, but regards intercapillary glomerulosclerosis and diabetic retinopathy as manifestations of the same pathological process in the two organs, modified by the different anatomical structure of each.

Appel (1950) considers the contemporaneous presence of diabetes and hypertension to be a consequence of a central disorder. The peripheral organs, the pancreas, and the kidneys would be terminal members of the chain, and changes occurring in them would have no causal inter-relation but would be parallel symptoms of the same basic disease.

We have shown that retinal aneurysms occur in connection with
arteriosclerosis, nephrosclerosis, nephritis, and diabetes, and have noted their presence in arteriosclerotic changes without any renal lesion. They have also been found to occur in association with nephritis, even when no other vascular changes could be demonstrated either macroscopically or microscopically. This suggests that the aneurysms have not developed as a consequence of hypertension, arteriosclerosis, renal changes, hyperglycaemia, or changes in the pancreas, but as a result of the disorder in the central regulation which is common to these diseases.

Central disorders differ in different diseases, although there are similarities. The occurrence of identical changes, such as aneurysms, is evidence of a close relationship, but the fact that the aneurysms do not appear in all patients suffering from the diseases we have studied, proves the variable character of the disorder even in the same disease.

While we are not justified in presuming that the diseases under consideration are different manifestations of the same process, it is clear that one can no longer recognize distinct borderlines between them. The central dysfunction does not always originate in a central factor. There is abundant evidence that impulses from the periphery may cause central disturbances, which in their turn either give rise to new changes in the periphery or aggravate those that have been produced earlier. This process has been reported in connection with pregnancy, infectious diseases, and injuries to peripheral organs. Renin and hyperglycaemia are known to give rise to central disorders which effect an exacerbation of the changes in the periphery, so that a vicious circle is produced. Boyd and Lewis (1938) and Platt (1942) showed that a unilateral renal lesion caused by a local process may give rise to a retinopathy which is cured after removal of the damaged kidney. Although here a local disease of a peripheral organ produced changes in another peripheral organ, it may be supposed that the changes developed through the medium of a central disturbance.

Many diseases, therefore, seem to be traceable to a disturbance of the central regulation caused either by a purely central factor or by an external one. Inter-relation may be noted between the central factor and the peripheral organs both in the centrifugal and in the centripetal direction.

**Summary**

An investigation has been carried out to ascertain the incidence of retinal micro-aneurysms in non-diabetic diseases, which, like diabetes, are associated with retinopathy.

One hundred and forty-three pairs of eyes were examined from a series of patients with arteriosclerosis, nephrosclerosis, and nephritis. Retinal micro-aneurysms were found in each group. Two types of aneurysms were noted: a localized spherical type, and an elongated,
fusiform, varicose type. There was no clear difference between the formations occurring in different diseases. It was found that aneurysms may appear in nephritic patients in the absence of generalized arteriosclerosis, and conversely that arteriosclerotic patients may develop them without exhibiting any renal changes.

In the arteriosclerotic group, micro-aneurysms were most frequent in the youngest patients. In the nephrosclerotic group they were more common in the oldest patients. In nephritis they were evenly distributed in all age groups. The results are compared with those already reported in the literature.

Aneurysms are not, apparently, developments due to hypertension, arteriosclerosis, renal disease, hyperglycaemia, or pancreatic changes. It is supposed that the aneurysms are caused by the disturbances in the central regulation which occur in these diseases.

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Retinal Micro-Aneurysms in connection with Generalized Diseases causing Retinopathy

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doi: 10.1136/bjo.35.9.560

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