

V. DISEASES OF THE RETINA.

1. *The pathology of diabetic retinopathy.*

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PART I: CLINICAL.

THE literature of diabetes in its relation to the eye consists largely of a discussion of three questions :

- (1) Is "diabetic retinitis" a clinical and pathological entity, distinct, for example, from the retinopathy of hypertension?
- (2) Is there a necessary relationship between diabetic retinitis and hypertension?
- (3) What part do the retinal vessels play in the production of the retinal changes?

Whatever answer is given to the second and third questions, there is an almost general consensus of opinion that diabetic retinitis is a clinical and pathological entity; and the characteristic or typical picture of diabetic retinitis may be described in the following terms :

The retina as a whole, and the optic papilla, show no evidence of oedema. *Exudates* take the form of white specks, at first discrete, but tending to coalesce to form spots and patches of a solid, yellowish-white lardaceous or waxy appearance. These are situated, for the most part, in the central area of the fundus, and sometimes simulate, in their distribution, the zonular exudates of retinitis circinata. *Haemorrhages* are mostly round or polygonal in form, and may be roughly described as dots and blots. The smallest, no larger than the diameter of the perimacular vascular twigs, are apparently round, sometimes even globular, as indicated by the presence of a central reflex, while others, which might be described as petechiae, are round, polygonal or linear in shape, and not, as a rule, larger in diameter than one of the principal retinal veins.

The haemorrhages, like the exudates, occur principally in the central region of the fundus. In the more extreme cases both may be more widely distributed, and gross and massive haemorrhages, both intra- and pre-retinal, may occur.

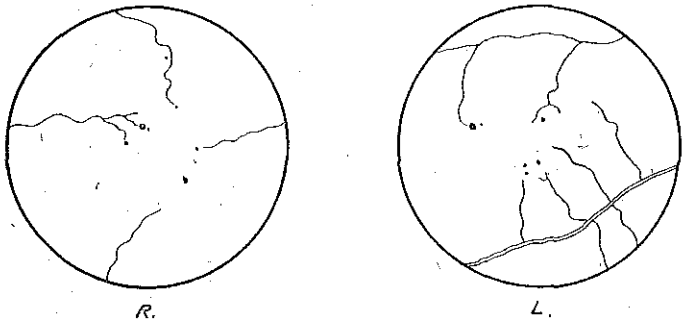
The "typical" form of diabetic retinopathy may occur even when the diabetes is associated with general hypertension; but where

hypertension is a pronounced feature of the case, the fundi are more likely to present both the diabetic features referred to, and the oedema, exudates, haemorrhages and vessel changes characteristic of hypertensive retinopathy.

Recent investigations, the result of which have not yet found their way into the text-books, show that the retinal complications of diabetes mellitus occur in at least two other forms, the first consisting of *haemorrhages* alone, and the second, of a very striking series of changes in the retinal *veins*, which are usually, but not necessarily, combined with haemorrhages and exudates.

In our view, neither of these three pictures can be confused with that of angiospastic or hypertensive retinitis. In the latter oedema

FIG. 25.



John Y—, aged 44, diabetic. On examination "punctate haemorrhages round the macula."

and diffuse albuminous extravasation is common; the haemorrhages, often spindle- or flame-shaped, tend to surround and radiate from the disc, or to form irregular patches associated with areas of white exudate; and the punctate exudates, though confluent, have not the waxy character of those seen in diabetes. Above all, the visible vascular changes are mainly or entirely confined to the retinal *arteries*.

Possibly in all these cases the term "retinitis" is a misnomer, if it is intended to imply the presence of an inflammatory process, and in this communication we adopt the term "diabetic retinopathy," which is certainly more appropriate when we include the two atypical conditions referred to above.

The recognition of the fact that there are diabetics in whom small retinal haemorrhages are the sole ophthalmoscopic change seems to us to be of the utmost importance; for there is reason to believe that these haemorrhages are the earliest ocular sign of the disease,

and that they may exist for a long period before the appearance of the grosser changes, which often draw attention to the diabetic state. If treatment is to be effective, any sign which leads to early diagnosis is of special value.

Several authors have called attention to the occurrence of retinal haemorrhages as the first or only evidence of diabetes (Gray, 1933; vom Hofe, 1938). In our experience they occur most characteristically in or close to the macula, as minute dark red dots, which are quite readily overlooked (Fig. 25). Naturally they are not so easily observed as the white spots of exudate of similar size. They are seen most easily with a narrow focused beam of light, and it is often necessary to dilate the pupil.

It must be admitted that sometimes there is a doubt as to whether we are justified in referring to these minute lesions as haemorrhages. When they present no central reflex, and have no visible connection with the blood-vessels, we may accept them as haemorrhages; but when they have a spherical form, and are attached, as they so often are, to the finest perimacular venules, like berries on a twig, we are probably dealing with aneurysms. We have no doubt that both lesions occur, but the differentiation of haemorrhages and aneurysms of such small size is not always possible by ophthalmoscopic examination alone, and, as we shall see, even microscopic investigation may leave us in some doubt.

The following cases illustrate the occurrence of these small haemorrhages as the principal feature in the early stage of diabetic retinopathy:

James B—, aged 19, diabetes mellitus of six years' duration, well controlled throughout. Receiving 12 units of insulin daily. Blood pressure: S. 110; D. 80. No visual complaint. Pupils a little irregular in outline from presence of posterior synechiae. In the right fundus, minute punctate haemorrhages to the number of about a dozen round the fovea. A few of these apparently strung on a fine venous twig up and in from the macula. One or two dark round haemorrhages, slightly larger, and one of mossy appearance, about three vein-breadths in diameter. In the left fundus a few minute punctate haemorrhages. Both discs normal, and no vessel changes visible in either eye.

Mrs. P—, aged 45. Mild diabetes of 12 years' standing, but controlled. Myopia: R.E. — 6.5 D.; L.E. — 5 D. When first examined, 15.iv.37, retinal vessels enlarged and tortuous. No sign of sclerosis. No haemorrhages or exudates. Corrected V.A. normal. Under constant observation without change in fundi till 14.iv.42, when a few small punctate haemorrhages appeared close

to the macula. These still appear and disappear from time to time. No exudates have been observed.

John Y—, aged 47. Diabetes of ten years' duration. Under treatment seven years with good response. In the right eye a number of small punctate haemorrhages, one or two of globular form, grouped round the fovea, and apparently arising from small terminal venules. In the left eye similar small haemorrhages along with some larger round haemorrhages, and one flame-shaped, outside of the macular area (Fig. 25). A few greyish-white specks within the area centralis in both fundi. R.V. = $\frac{6}{8}$, L.V. = $\frac{6}{8}$.

In a number of patients examined in routine eye practice the discovery of these small haemorrhages and/or aneurysms has caused us to suspect the presence of diabetes a diagnosis subsequently confirmed. In several such cases the urine was sugar-free, but the blood showed sugar in excess.

Contrary to the view of those writers who assert that diabetic retinal changes occur only in the subjects of arteriosclerosis (Duggan, 1938; van Duyse, 1938), it has been our experience that arterial changes are by no means characteristic of the diabetic fundus; indeed it is usual to find no more arteriosclerosis than one would find in non-diabetic subjects of the same age. There is, however, very definite evidence of involvement of the retinal *veins*, and their tributaries. Thus, in about one-third of the cases of diabetes submitted to routine examination, the principal retinal veins were unduly large and tortuous. The minute haemorrhages, to which we have referred, apparently originate in the smallest visible (and sometimes ophthalmoscopically invisible) venules. Even the larger round and petechial haemorrhages, which are a characteristic feature of the classical diabetic retinopathy, are deep in situation, and almost certainly from the venous side of the capillary plexuses.

A still more striking illustration of the greater incidence of pathological changes on the retinal *veins* is afforded by a group of cases which received very little notice until about six years ago, and in which the fundus picture is dominated by venous changes of a very special character.

Nettleship (1888) described the case of a diabetic, aged 48, whose retinal veins showed considerable distension. Several medium-sized vessels appeared near the fovea, as if emerging from the choroid, and divided into a network of minute vessels forming loops in the vitreous, and beset with aneurysmal swellings. In the case of another man, aged 58, a large dilated ascending branch of the central retinal vein presented a beaded appearance.

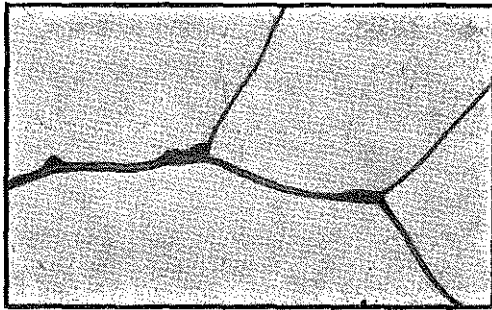
Gray (1931) refers to the appearance of "beading" of the retinal veins. Expansion and varicosities of the veins were mentioned by

Braun (1936, 1937), and Mylius (1937) considered that stasis or blockage in the retinal veins was the cause of the retinopathy of diabetes.

The first communication devoted to the more characteristic changes in the retinal vessels in diabetes was that of Bonnet and Bonamour (1938), dealing with three cases complicated by the presence of hypertension. They state that in such cases the vessel changes fell chiefly upon the veins, and refer to irregularity in calibre, segmented dilatations, diverticula, and white sheathing of the veins.

O'Brien and Allen (1940) draw attention to the scanty references to changes in the retinal veins in diabetes, and in a study of 21

FIG. 26.



"Example of change in the retinal veins in diabetes."

cases, every one of which showed varicosities of the larger retinal veins, there were also frequent alternations of constrictions and varicosities, and sometimes bilateral sheathing.

In the same year Agatston (1940) contributed a histological study of diabetic retinitis, and pointed out that the vessel changes are more specific in the capillaries and veins than in the arteries.

Gibson and Smith (1941) described as examples of "medial phlebosclerosis" some of the venous changes we are now considering, observed ophthalmoscopically as kinks, tortuosities, nodular dilatations and new vessel formations.

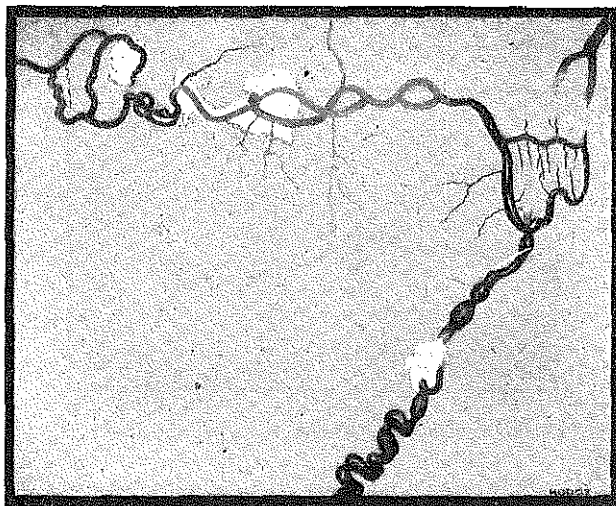
Unfortunately none of the papers referred to tried to correlate the ophthalmoscopic and microscopic changes in the same case.

The illustrations (Figs. 26 to 29) will show the principal features of the venous changes in the cases observed during the last seven years in the Western Infirmary and the Tennent Institute. These changes were mentioned in the discussion on Bedell's contribution

in 1939, and were also briefly referred to in the Mackenzie Memorial Lecture (Ballantyne, 1942).

The formations may be described as general and localized expansions, beading, loops, kinks, diverticula and so on. Networks of fine vessels in or on the surface of the retina (*rete mirabile*) and tufts of vessels projecting into the vitreous are often found; but these occur also in hypertensive cases, especially where there has been gradual occlusion of a division, or even of some small branch, of the central retinal vein, and are therefore not specifically diabetic. But

FIG. 27.

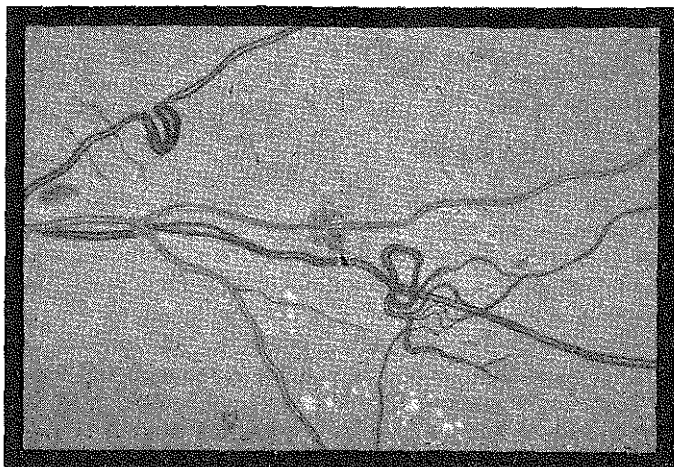


“ Example of change in the retinal veins in diabetes.”

the changes depicted in these fundus drawings seem to be pathognomonic of diabetes. They belong to the principal veins; and many of the loops and coils are of even greater diameter than the normal vessels. One feature that is often noted is that a vein may show an expansion or series of expansions some distance from the disc, and as suddenly resume its normal diameter at a more distal point (Fig. 29). A mechanical explanation of these changes of calibre has not been found, but they should probably be correlated with the changes in the large veins to be referred to later under the title of phlebosclerosis.

It will be noted that, unlike what happens in arterial disease, most of the abnormalities here consist of *expansion* of the veins, or the

FIG. 28.



" Example of change in the retinal veins in diabetes."

FIG. 29.



" Example of change in the retinal veins in diabetes."

opening-up of new channels. They suggest the occurrence of long-continued obstruction, probably partial occlusion, of the principal veins, or of the central vein itself. But this could not be accepted as a complete explanation of the phenomena. In the first place, although diabetes is one of the recognized causes of thrombosis of the central vein, it is, according to the figures given by G. Coats and Foster Moore, by no means the most common; whereas, of some 17 cases in which we found the venous changes in question, all but one were diabetic. Further, in thrombosis of the central vein there is uniform distension and tortuosity of all the retinal veins, whereas in this type, one alone or several of the retinal branches may be affected; and the localized character of the venous changes is not seen in cases of thrombosis, either in the trunk of the vein or in any one of its retinal branches. The general picture, and the association of these changes with the *rete mirabile*, vitreous vascular tufts and haemorrhages, show that stasis in the veins is an important factor; but a further factor is needed to account for the local disease of the vessel walls which causes the expansions, loops, by-passes and other abnormalities. This factor, whatever it may be, must be intimately linked to the diabetic state. That arterial hypertension is not an essential factor is proved by the facts that it was present in only one-half of the cases, that the venous changes in question are quite unfamiliar in the many cases of arterial hypertension which are continually under observation, and that in general the vascular retinal changes in hypertension fall principally on the arteries, and those of diabetes mainly upon the veins.

So far, the nature of the agencies which damage the vein walls has quite eluded discovery, although much research has been devoted to the attempt to find the cause or causes of diabetic retinopathy. Metabolic changes in the walls of the vessels have been attributed to the hyperglycaemia (Agatston, 1940). Elwyn (1941) takes the view that the increased blood-sugar level causes a weakening and dilatation of the terminal vessels, with consequent stasis which leads to the haemorrhages and other changes. Mori (1930) pictures the occurrence of chemical changes in the intra-ocular fluids which cause, among other effects, increased permeability of the vessels, whereby metabolic products in increased amount reach and damage the nervous elements in the retina.

On the other hand, clinical observation indicates that there is no correlation between these vascular conditions and the severity or duration of the disease, the character of the diet, the administration of insulin, and the response of the disease to treatment.

Mylius (1937) refers to toxic substances produced by stasis in the veins. He also believes in the injurious effect of excessive fat in

the diet, while vom Hofe (1938) finds no relation between diabetic retinopathy and excess of blood sugar, acetone, lipoids or residual nitrogen.

As will appear later, our own investigations reveal histological changes in the endothelium of the smaller veins, which may be the starting-point in the pathogenesis of diabetic retinopathy.

PART II: HISTOLOGICAL.

It has frequently been pointed out that histological investigations in cases of "pure" diabetes have been scanty and inconclusive. This is not surprising when we consider that the pathological changes in the eye may have passed into an advanced phase before the pathological material can be obtained by excision (e.g. for secondary glaucoma) or at autopsy, and that the observed conditions may not be such as have been observed with the ophthalmoscope. Further, even if early material can be obtained, we are met with the usual difficulty of identifying small ophthalmoscopic lesions with those in our pathological sections; and where a patient in an early stage of diabetes dies of intercurrent disease, it is frequently the case that there has been no ophthalmoscopic examination.

Here the *post-mortem* investigation of the fundus with the slit-lamp and the examination of the unstained retina in bulk under the microscope come to our help.

The pathological material on which the histological part of this investigation is based was derived from:

(a) Cases of diabetes which died without ophthalmoscopic examination, and in which no fundus lesions were found on slit-lamp examination after death—two cases.

(b) Cases in the same group, in which changes were discovered in the fundus by slit-lamp examination after death—four cases.

(c) Cases in which fundus changes were observed both before and after death—two cases.

(d) Cases of diabetes in which the eye, known to be the seat of fundus changes, was excised during life—one case.

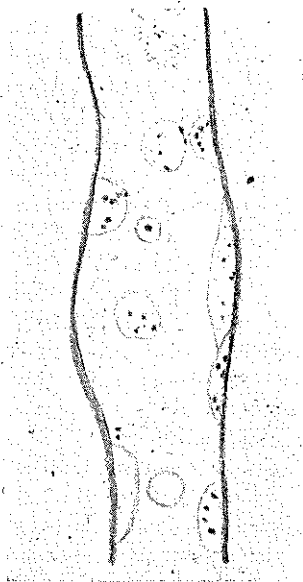
In the last case the whole eyeball was obtained, in the others only the posterior halves of the eyes and the attached optic nerves. The fixation fluid was 10 per cent. formalin.

On the histological, as on the clinical side, the attention of investigators has been limited for the most part to the fully established picture of diabetic retinal disease. Thus some of the earlier changes have been missed, and not only for this reason, but also because the routine methods of fixation and embedding involve the use of fat

solvents, which destroy important elements in the vascular and tissue changes.

Many of the findings which we have arrived at, and which we think worth putting on record, were made possible by the examination of the retina in bulk, unstained or stained with scarlet red; in some cases stained afterwards in bulk with weak Nile blue or haematoxylin. After examination of the bulk specimen on the flat these selected pieces of retina were embedded and cut in gelatin and the sections treated with nuclear stains. We have tried to

FIG. 30.



Diabetic changes in the retinal vessels. Fatty granules and droplets in endothelial cells. Retina in bulk, viewed on the flat, stained with scarlet red.

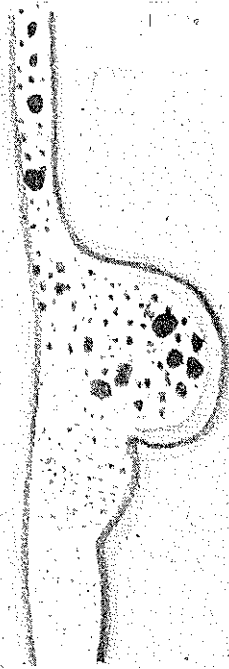
discover the earliest and minimal changes, especially in cases of diabetes without hypertension.

We have, of course, to discount the fact that in advanced age fat is found in the media and adventitia of the vessel walls, as well as in the ganglion and glia cells; but we have found characteristic lesions in the eyes of diabetics in which no diabetic retinal changes were discovered by ophthalmoscopy or by routine histological methods, as well as in cases with advanced vascular disorders and those with gross degenerative changes.

Endothelial Changes.

Examining the retina, unstained, on the flat, we can recognize the smallest vessels. Even the endothelial cells of the capillaries can be seen by suitably stopping down the iris diaphragm. Most of the capillaries and minute vessels are empty, but under scarlet red staining some contain pinkish fatty serum and the endothelial cells are sprinkled with red fatty droplets. The droplets are of varying

FIG. 31.



Retina in bulk. Stained with scarlet red. Fatty deposits in vessel walls.
Formation of aneurysms.

size and density, most of them about 1 to 2 μ or even smaller (Fig. 30). Sometimes they are arranged like a belt around the lumen of the vessel. In contrast to the findings in similar material from cases of hypertension, the fatty droplets are found in the inner layer of the vessel wall leaving the adventitia free.

Sometimes, where the fatty infiltration of the endothelium is of notable degree the wall of the vessel has become ectatic, forming an actual aneurysm (Fig. 31). The endothelial deposits may be

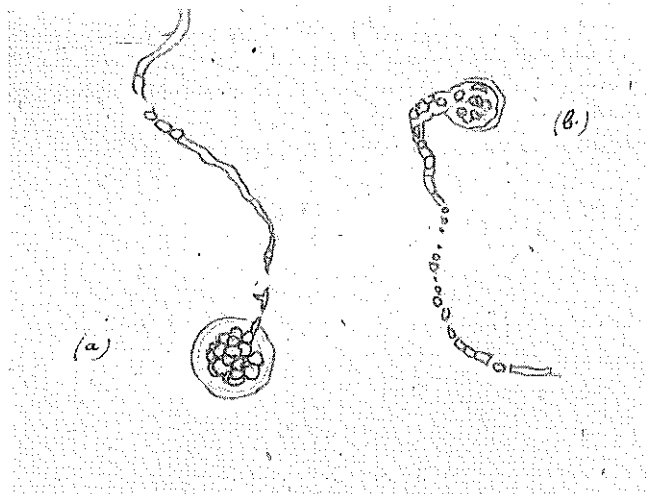
especially dense at junctions and bifurcations of vessels. It seems possible that the walls at such points are subjected to a species of physiological trauma, which may determine the site of the fatty change. Such a mechanism is assumed in the case of infective lesions of vessel walls.

The discovery of these fatty changes in the vascular endothelium, even in cases of diabetes presenting no other retinal lesions, leads us to the conclusion that they are characteristic of diabetes, and that they are among the earliest, if they are not the earliest, histological evidences of that disease.

Gross Vascular Changes.

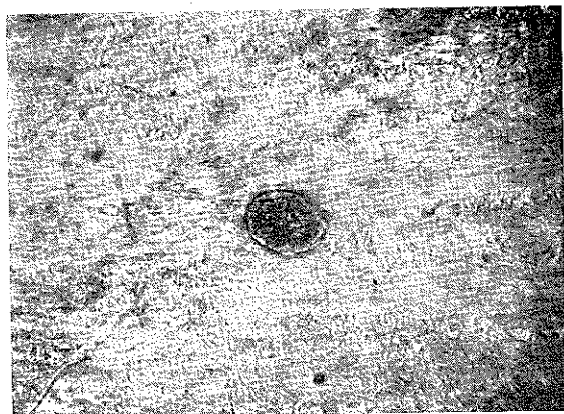
Fatty changes in the vessel walls seem to predispose the vessels to the formation of aneurysms, and we observe these frequently, both in the examination of the fundus with the corneal microscope and slit lamp, and in microscopic preparations seen on the flat. Here they appear in two forms, either as globular bodies obviously attached to the vessels (Fig. 32), and often in series like chains of beads, or as isolated spherical bodies consisting of closely packed red blood-corpuscles enclosed within a capsule and without any discoverable connection with a vessel (Fig. 33). The former we have no difficulty in regarding as aneurysms; the latter, for lack of a better term, we refer to as "encysted haemorrhages." In these the thickness of the wall varies a good deal. The figure shows a not uncommon form from an uncomplicated case of diabetes. They are usually situated deeply in the retina—about the level of the outer molecular layer—and, like the definitely aneurysmal bodies, are usually associated with patches of diffuse retinal haemorrhage. Both forms of spherical bodies give the fatty reaction with scarlet red. We have identified the discrete unattached spherical bodies with the small round spots at the macula which are described clinically as punctate haemorrhages (Fig. 25), but some of them, at least, are probably aneurysms whose link with a parent vessel has disappeared, or is too transparent to be visible. The density of the containing wall seems to indicate that the bodies have been in existence for some time, and it is quite possible that the vessel of origin has atrophied. We have still to satisfy ourselves as to the identity of these with the round, sharply enclosed collections of red blood-corpuscles, most of them without recognizable vascular connections, which are often seen in the outer molecular layer in sections. Nothing resembling them has, so far, been observed in the superficial layers of the retina in vertical sections of the retina.

FIG. 32.



Diabetes. Retina in bulk, unstained. Aneurysms attached to capillaries.
 (a) 35, (b) 26 μ diameter.

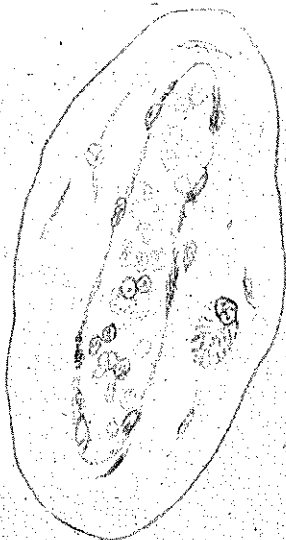
FIG. 33.



Diabetes. Retina in bulk, unstained. Aneurysm or encysted haemorrhage,
 without visible attachment to vessel.

Among other well-established changes in the vessels we find both arteriosclerosis and phlebosclerosis. The latter shows itself first as a sometimes patchy fibrillary thickening of the wall of the vein, at a later stage replaced by a still thicker, hyaline structure. Some very extreme examples of this change have been met with (Fig. 34), and in its minor degrees it is common. Microphotographs of the crossing of a vein over an artery show very well the contrast in the condition of the vein and artery.

FIG. 34.



High degree of phlebosclerosis. Wall greatly thickened and completely hyalinized.

Networks of venules or capillaries, even finer than those seen in the ophthalmoscopic picture of *rete mirabile*, are well brought out in examination of the unstained retina in bulk, in a manner which usefully amplifies the view obtained from retinal sections (Fig. 35). They are seen to be both intra- and pre-retinal. No doubt they are to some extent the result of the dilatation of pre-existing capillaries, although some of them, the pre-retinal ones, for example (Fig. 36), must be new-formed vessels.

Retinal Tissue Changes.

In a diabetic retina without gross tissue or vascular changes groups of bright red fatty droplets were found, 7 to 10 μ under the

retinal surface, while 40 to 50 μ deeper larger but less distinct drops appeared, among shadowy outlines of cells which seem to belong to the boundary between the inner nuclear and outer molecular layers. Here and there fat droplets were found in rows between the nerve-fibre bundles. In the unstained retina we found at this level individual red blood-corpuscles as well as greyish-brown granular masses filling the spaces between the nerve-fibre bundles. According to E. Wolff these interspaces in the normal retina are

FIG. 35.



Rete mirabile in advanced case of diabetes. Low-power view. Unstained retina in bulk. Diffuse hæmorrhage and micro-aneurysms are also present.

occupied by the feet of Müller's fibres, and the appearance in question may represent Müller's fibres acting as carriers of the fatty granules. About 30 to 50 μ deeper we found in the same case glassy patches associated with old diffuse hæmorrhage.

Portions of this retina, after staining in bulk with scarlet red, were embedded in gelatine, cut in frozen sections, and afterwards stained with weak hæmatoxylin or Nile blue sulphate. In these sections we found not only intensely stained fatty droplets, but also bright sky-blue patches and purple masses tending to assume a honeycomb form. We are not in a position to differen-

tiate these three substances in regard to their chemical nature, but the blue and purple masses appear to be of a non-fatty character.

FIG. 36.



Pre-retinal network of new formed vessels embedded in matrix of gelatinous-looking tissue.

FIG. 37.



Cholesterin crystals—two types—in degenerate eye of diabetic. Crystals abundant in vitreous and in subretinal fluid, as well as in retina.

Mallory-stained sections of the same retina showed masses in the external molecular layer which might be clumps of red blood-corpuseles undergoing a transition into masses of so-called retinal exudate.

Retinal Disintegration—the Most Advanced Stage.

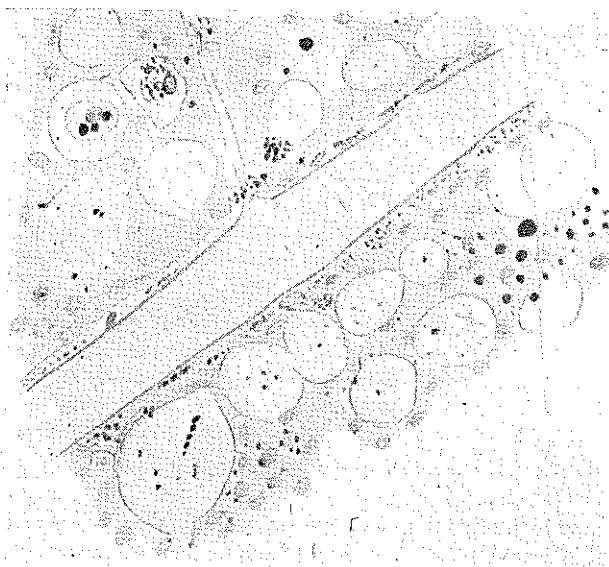
We had an opportunity recently to study an eye from a diabetic man, aged 65, who has been under observation for the past 15 years. Clinically he was known to have, in both eyes, retinal haemorrhages, new-formed vessels and white plaques of exudate. Latterly he had a complicated cataract with iridocyclitis. The excised eye revealed a detached retina, with turbid vitreous and subretinal fluid. The vitreous body was filled with cholesterol crystals, both sickle-shaped and in rhomboidal forms (Fig. 37). The retina examined in bulk was also full of these crystals. The vitreous contained also large vacuolated cells with a granular cytoplasm, as well as pigmented corpuscles. The retina was completely degenerated, cystic throughout, with fatty deposits widely disseminated (Fig. 38). The smaller vessels showed localized expansions.

An outstanding feature was the vascular network covering the greater part of the retina. The constituent vessels were at many different depths, and some loops projected as much as 100μ from the retinal surface.

The occurrence of such networks has already been referred to as a feature of a *post-mortem* specimen from a less advanced case of diabetes. The illustrations from that case showed that the *rete mirabile* consisted partly of an intraretinal part composed apparently of dilated pre-existent capillaries or venules, and a pre-retinal part (Fig. 36) derived from retinal veins which had penetrated the internal limiting membrane. The pre-retinal vessels, some of them like greatly distended capillaries, others with very thick walls and narrow lumen, were embedded in a deep layer of a primitive looking connective tissue. The picture might be described as a retinal pannus. At one point a mass of this tissue containing a few vessels projected forward into the vitreous. At another point the thickened internal limiting membrane seemed to split into two lamellae, embracing between them this connective-tissue layer with its vascular network.

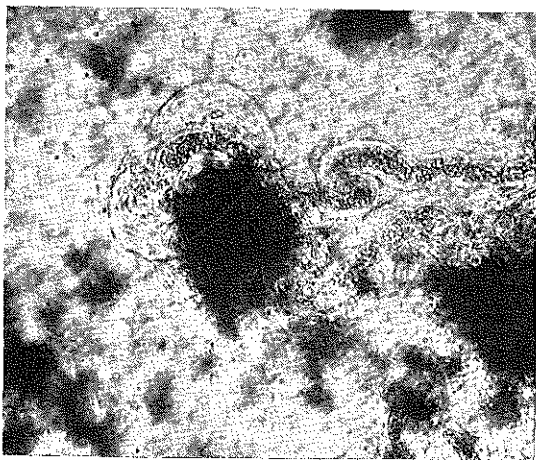
In the advanced case now under discussion these changes were present in a much exaggerated form. Here and there it was possible to find capillaries coming to a closed end—apparently the growing points of invading vessels. The vascular loops (Fig. 39) were embedded in a tenuous gelatinous-looking tissue which, in the Nile blue staining, was seen to form a very thick wall to the new-formed vessels, with a faintly fibrillary structure. Elsewhere it was merely a structureless matrix in which were embedded the vessels formed of simple endothelial tubes. A microscopic haemorrhage was found issuing from a point where a small vessel was

FIG. 38.



Advanced stage of diabetic retinopathy. Cystic degeneration of retina. Fatty deposits.

FIG. 39.



Loops of new built vessels on surface of retina with thick walls composed of delicate gelatinous-looking tissue.

blocked, and there seemed to be an attempt to establish a compensating channel. Some larger vessels were completely occluded and converted into yellowish bands covered with long streaks of pigment.

SUMMARY AND CONCLUSION.

From a clinical and pathological study of the retina in diabetes we are strengthened in our view that diabetic retinopathy is an entity distinguishable from hypertensive retinal disease. It may take several forms different from the familiar picture of "diabetic retinitis."

The earliest change so far recognized with the ophthalmoscope takes the form of minute punctate and globular effusions in and around the macula, and these may exist over a long period in the absence of retinal exudates and without changes in the visible retinal vessels. Ophthalmoscopically these haemorrhages (or aneurysms) are apparently related to the fine retinal venules around the macula.

The more obvious vascular changes in the diabetic fundus show a marked preference for the veins, and sometimes take somewhat grotesque forms which are not observed in association with hypertension or arterial disease.

In the histological approach the minimal pathological change, discovered even in eyes which showed no abnormality with the ophthalmoscope, is a deposit of fatty substances in the form of fine droplets staining with scarlet red in the endothelial cells of the retinal vessels, including the capillaries. These have been found even in retinae without haemorrhages.

Ectasiae, proceeding to the formation of aneurysms, are prone to form at points where the fatty change is most pronounced. It is often difficult to distinguish these aneurysms from the spherical and encysted collections of blood-corpuscles, which, like the aneurysms, are deeply situated and give the fatty reaction with scarlet red. Both of these can be distinguished from round haemorrhages which have no limiting capsule. Blood effused in a loosely built tissue like that of the external molecular layer naturally assumes the spherical form.

Swelling of the affected endothelial cells narrows and blocks the lumen of the small vessels, and may be responsible for the formation of the networks of vessels seen at a more advanced stage. Some of the thin-walled veins penetrate the internal limiting membrane and produce a form of pre-retinal pannus, the vessels of which are embedded in a remarkable gelatinous-looking tissue.

The ophthalmoscopic evidence that there is a greater incidence of the vascular changes on the veins than on the arteries is confirmed by histological studies. Phlebosclerosis is seen in two forms—an unsymmetrical fibrillary thickening of the vein wall with normal or increased lumen, and a great thickening with complete hyalinization, and narrowing of the lumen.

Special staining methods brought out the presence of three different forms of retinal exudate, one of which was of a fatty nature.

In a diabetes of long duration, in addition to these vascular and tissue changes, gross degeneration of the retina, detachment of the retina and abundant cholesterol crystals in two forms in the vitreous and the subretinal fluid were found.

We conclude that some form of chemical agents in the bloodstream, other than those peculiar to hypertension and renal disease, and almost if not quite specific to certain cases of diabetes, are responsible for the pathological changes in the vessels, and that the changes in the small vessels, especially the veins, venules and capillaries, may well be the starting-point of a sequence of events leading to all the phenomena which are covered by the term "diabetic retinopathy." The nature of this noxious agency has not been discovered.

We are naturally tempted to refer to the gross changes in the principal veins as an advanced stage of diabetic retinopathy, but on our present information such a description would not be justified. These venous anomalies may occur in the absence of the haemorrhages and exudates which we consider to be characteristic of diabetic retinopathy. We have not been able to observe them developing out of an earlier phase, and we have the baffling fact that they may occur in cases of diabetes described as mild and well controlled. Although the prognosis *quoad visum* is unfavourable in the extreme, and progressive deterioration of the eyes is often observed, this bears no relation to the prognosis *quoad vitam*.

The recognition of the diabetic significance of "punctate haemorrhages" around the macula, and the gross venous changes referred to, is of considerable importance in diagnosis.

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