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Donald A. Argo
University of Nebraska Medical Center

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DIABETIC MICROANEURYSMS

I. Introduction

In diabetes mellitus there are several ocular signs that may be seen. The one seen first and most often is that of microaneurysms. This paper will deal with a literature review of this subject.

II. Review of Literature and Discussion

Ballantyne[3] has reported that the first description of retinopathy was that reported in a diabetic patient in 1851 by Jaeger just five years after Helmholtz had introduced the ophthalmoscope. During the next twenty years little was done in the study of retinopathy, but what was done was reported in 1875 by Leber as stated by Larsen[17]. His conclusion was that the retinopathy was due in part to the diabetes and in part due to the nephritis produced by the diabetes.

Nettleship[22] reported in 1882 a person with diabetes who was blind in one eye and in the other eye, by ophthalmoscopic exam, there could be seen what was described as white spots and hemorrhages. In the post-mortem examination of the fundi, there could be seen hyalin thickening of the arteries, several aneurysmal dilatations of the vessels, some retinal hemorrhages and some waxy and granular material in the retina. This was the first information of histologic studies of a clinical case of diabetic retinopathy. Nettleship again in 1886[21] and 1888[20] reported his clinical findings in two different cases of diabetes. In one he reported small white spots and hemorrhages in the retina. The other was a forty-eight year old male whose vision did not

improve when his diabetes was treated. Nettleship could see in this retina yellowish-white clumps of material, retinal vein distention, a few scattered blood spots, retinal hemorrhages that were flame shaped and some were round, and the formation of new blood vessels in the vitreous. In some of the new vessels in the vitreous, he could see some fine loops and on some of the loops he could see small swellings. Nettleship at that time thought that the retinal changes were due more to diabetes than they were to the nephritis.

From 1890 to 1943, almost every investigator thought the cause of the retinopathy was due either to hypertension, arteriosclerosis or renal disease. Also during this time, it seemed as if much of the interest was lost in the diabetic retinopathy even though insulin was introduced in 1922. About the only really important work that was done before 1943 was Kimmelsteel and Wilson's work in 1936 showing the typical lesion of the diabetic glomerulosclerosis which carries their name today.

There were only a few histologic studies of diabetic eyes made before 1943, but in 1943 Ballantyne and Loewstein[3] published their findings in diabetic retinopathy. Their findings by light microscopic studies showed expansion and series of expansions of veins some distance from the optic disk, hemorrhages, beading, loops, kinks, and diverticula along the vessels. By staining and section of the vessels, he noted fat in the endothelium of the smaller vessels, after which the walls became ectatic and an aneurysm would form. He also noted encysted hemorrhages, arteriosclerosis and phlebosclerosis

with the walls of vessels greatly thickened and completely
hyalinized. There were punctate hemorrhages around the macula.
With Ballantyne and Loewstein rediscovery of the retinal
microaneurysms, there have been extensive histologic and
clinical studies done to try to clarify come of the pathogenic
factors in this problem.

The incidence of the retinopathy before the introduction
of insulin therapy in 1922 was found most often in diabetics
over the age of forty years who had mild, easily controlled
diabetes. At that time, the juvenile diabetics did not develop
retinopathy as they did not live long enough. It is now shown
that the relationship probably is between how long a person
has had diabetes and not in how severe it is. Today with the
duration of the disease increased from two to over twenty years,
the incidence of retinopathy has increased from two to forty-
nine per cent. In diabetics under the age of sixteen to eighteen
years, retinopathy seldom occurs no matter how long the disease
has lasted. After the patient has had diabetes for over twenty
years, the incidence ranges from between twenty to one hundred
per cent.[1]

Root[26] and several others have found that the incidence
of retinopathy in diabetics who had been poorly controlled
was around ninety per cent but only eight per cent in well
controlled diabetics and juvenile diabetics. Microaneurysms
are seldom seen before diabetes has lasted about ten years and
seldom develops before the age of sixteen to eighteen years.
Aneurysms in middle-aged diabetics occur mostly after five to
ten years and in older diabetics they are often seen two to

five years after the disease is demonstrated.

Retinopathy is divided into five stages:

Stage I: Microaneurysms resembling small round hemorrhages appear near the optic disk and macula. Slight dilatation of veins may be present but the arterioles are normal.

Stage II: Veins are dilated, and scattered, small waxy-yellowish hard-appearing exudates are seen. This is addition to the microaneurysms of Stage I.

Stage III: In addition to Stage II findings, there are cotton wool patches usually much smaller than the optic disk. The cytoid body may be senn on histologic section. This phenomenon is the result of ischemic infarction of a terminal arteriole and appears as an eosinophlic granular, disk-shaped area in the nerve fiber layer representing swollen glial cells.

Stage IV: Marked venous changes are present venules are dilated and cyanotic with a link-sausage appearance and vessel sheating. Large and small hemorrhages are prominent and may occur within any layer of the retina or become pre-retinal.

Stage V: Large retinal and pre-retinal hemorrhages and hemorrhages into the vitreous are present. The latter gradually absorb, leaving fibrous scar tissue with new vessel formation. This is the picture of retinitis proliferans. If contraction of the scar tissue occurs, it may detach the retina, leading to ultimate total loss of vision.

Some of the other findings in diabetic retinopathy according to Bloodworth[5] are: Cotton wool plaques: These are tiny white superficial retinal infarcts. Microscopically they are disc-shaped foci of nerve fiber layer, that have thickened and necrosed. They contain the cytoid bodies which are globular and strongly acidophilic. They measure from ten to twenty microns in diameter. Probably these are protein-aceous aggreates, situated soley in the nerve fibers and ganglion cell layers. The abundance of the cytoid bodies parallel the extent of the vascular disease. The origin of the cytoid bodies has been assumed to the residue of hemorrhage, transudates, degenerating glial cells and swelling nerve fiber stumps. Toussaint[27] found a disappearance of the cells in the vicinity of the cytoid bodies and because of the associated vascular changes, he thinks, they are ischemic necrosis of the inner retinal layers as does Friedenwald[14] and Ashton[2]. Some workers also think that these retinal changes are caused by hypertension rather than from diabetes.

Deep waxy exudates or hyaline material is found ramifying irregularly through the outer plexiform layer with irregular atrophy and degeneration of neuroectodermal derivatives. This material is clustered in the perimacular region in areas of acellular capillaries. The hyaline material has the same stainability with eosin and PAS as does subretinal serum. Thus it is felt that the hyaline material is serum. The hyaline material is most marked in cases with severe vessel changes and it is absent if the vessels are normal. The defect must affect either the capillary itself or focal groups of

glial cells which completely surround the retinal capillaries.

One of the first changes seen in diabetic retinopathy is that of the microaneurysm. The other changes that are found are probably secondary to the microaneurysm and the other microscopic vessel changes. Such vessesl changes and the microaneurysms are thus the most important changes of the diabetic retinopathy picture that needs to be studied.

As a starting point, a person must find out a few things about the normal retinal blood vessels.

Francois and Neetlen[13] have grouped the capillaried into four systems:

The first is the classic system, where there is a transition from arteries to veins via canaliculi which increase in number as their diameter decreases. There are no direct communications between the arteries and veins with a diameter exceeding that of a capillary. Such a capillary system is characteristic of the normal retina with the exception of the peripapillary region, macular region, and the extreme periphery.

The second is the Chambers Zweifach network. Which is that of the arterovenous transition being formed by a wider-canal with the diameter of an average precapillary. From this transition, very fine capillaries extend in all directions. Such a capillary system is found in the peripapillary retina, the optic nerve, and nasal part of the intracranial optic nerve.

The third system is the direct precapillary transition which is a single wide canal also of precapillary dimension

but without any dependent true capillary network. This direct noncapillary artenovenous transition is found in the pericapillary parts of the retina.

The fourth type of capillary systems, the Sucquel-Hoyer anastomosis, is the same as the classic system but it has a more direct and wider communication between artery and vein. This system is not found in the optic pathways.

The study of the capillaries with electron microscopy has done much to help in the understanding of the changes in diabetic retinopathy. The normal capillaries are distributed in the three tissue layers; the nerve fiber layer, the ganglionic cell layer, and the inner and outer plexiform layer. The walls of the capillaries consist of endothelial cells, basement membrane forming the outer layer over the endothelial cells, the pericytes or mural cells and this is then surrounded by a glia cell with nervous tissue occuring on the outer side.

The endothelial cells are flat bodied cells. The nuclei are pale staining and protrude into the lumen of the capillary. They are arranged in a single layer with each endothelial cell being continuous and not marked with any pores in any part of it, although the cells have some thin spots in them. The cells are kept in close contact with the basement membrane. They are 500 A to 1 micron in thickness. The basement membrane is thicker in the capillaries in the eye than it is in any of the capillaries in the rest of the body. The basement membrane is in close contact with the endothelial cells on the inner surface and with the nearest glia cell on its outer surfacr. The pericytes or mural cells are a highly irregular shaped

cell which are enclosed in the basement membrane. The pericytes probably have dendriform of stellate processes which run parallel along or in a spiral fashion about the capillary much like the smooth muscle cells of the larger vessels. The nuclei are dark staining, spherical shaped and by their position protrude to the out side of the vessel.

The function of the mural cells is thought to be about the same as that of smooth muscle, as it has a superficial resemblance to that of the smooth muscle of the larger blood vessels.[19] Kawabara[16] has noted that in capillaries which have lost their mural cells, there seems to be an increase in the frequency with which red blood cells are found. The absence of red blood cells in normal capillaries most of the time would suggest a tonic effect from the mural cells. He also noted that new vessels will develop only from vessels which do not have mural cells.

Glia cells are the last normal cells found around the capillaries these cells have a body that is branched in various ways. Each capillary has around it several glia cells each with a large body and with terminal limbs extended far into the surrounding nerve tissue.

Since Cogan[10] has developed a new method of trypsin digestion, it has permitted the study of the cellularity of the walls and slo permits the observation of the vascularity of the capillaries in three dimension. These speimens were then stained with PAS, as the vessel will stain well with it.

In capillaries which appeared normal to opthalmoscopic examination, by light microscopy there were changes with increased reduplication of the basement membrane so there was a swiss-cheese appearance. The thickening of the basement membrane and the loss of the mural cells were the first changes that could be seen in the capillaries. Light microscopy of the capillaries show thin-walled capillary dilatation, some focal areas of capillaries showed diffuse or "varicose" dilatation. Others show degeneration with disappearance of all elements of the wall except for the basement membrane which remains to give a shadow-like reproduction of the original capillary bed much like an infart would demonstrate.[5]

The electron microscope studies showed a thickening of the basement membrane of the capillaries from a mean of 730 Å for the normal eyes, to 3,600 Å mean from retinas of diabetics. The basement membrane as a rule is thickest in the diabetics who have had the disease the longest.[10] The basement membrane has been noted to contain granuals and lamellar debris, this is probably from the breakdown of mitochondria and golgi apparatus. As the basement membrane is thickened, there is a gradual infiltration, for the most part, the basement membrane appears structure-less and homogeneous. In areas, red blood cells have been seen to diapedes through the basement membrane.[31]

There is a marked decrease in the extent of the ramification of the mural cells, with a final loss of the mural cells and their nuclei. From the site on the capillaries that the mural cell is lost there is a pale staining outpouching of

the capillary wall, these are called mural cell ghosts as
they are thought to represent the remains of the former mural
cell nuclei. The loss of the mural cells seem to result in a
pathologic shunting of whole blood through some of the
capillaries with total ischemia of the adjacent capillaries.[10]

The endothelial cells in the capillaries that have lost
the mural cells shows a proliferation in all early cases. In
the end stages, the endothelial cells undergo resolution
and degeneration which is most marked in the large aneurysms.[10]

The microaneurysms seen in diabetic retinopathy can be
divided into five types. The first type is a dilatation in
the capillary wall leading to a thin walled structure. A
later stage is a thick walled structure which becomes occluded
with PAS staining material. The second typed has a redupli-
cation of the basement membrane and the lumen is filled with
blood cells. The third type is a dissecting aneurysm with red
blood cells between the layers of the basement membrane. The
fourth type is a nondiabetic aneurysm, which are less numerous,
more peripheral in the retina and mostly thin walled. The
fifth is an extraretinal aneurysm most often seen in the
choroid and the brain.[1]

The microaneurysms are seen in the early stages of diabetics
retinopathy. They arise from capillaries with normal or
hyperplastic endothelial lining about foci of acullular and
presumably occluded capillaries. The microaneurysms form a
corona around the acullular zone which appears as a discreat
hole in the vascular network.

The early aneurysms are saccular outpouching, balloon shaped, thin walled, large cavities containing many erythocytes and leukocytes. The basement membrane by high magnification appears to be structure-less and homogeneous. There is no evidence of proliferation of endothelial cells early. These thin walled saccular aneurysms are thought to then become the thick walled hyalinized aneurysms seen in older diabetics. The thick walled aneurysms have proliferative endothelium along with the progressive thickening of the basement membrane. The composition of the basement membrane has the same histochemical composition as that of normal vessel walls which is PAS positive staining. The thickened basement membrane is concentrically laminated with numerous spaces between layers. The thickening of the walls ultimately leads to occlusion of the microaneurysms and loss of all their cells.

The distribution of the microaneurysms was found by Cogan[10] to arise from capillaries, terminal arteries, and small vessels and not just from venous side of the capillaries as had been thought. With very rare exception, the aneurysms were limited to the smallest vessels of the microcirculatory system. Kuwabara[16] noted that the shunt vessels which ophthalmoscopically presented as tortuous vessels had most of the microaneurysms and endothelial proliferation.

This loss of the mural cells and the thickening of the basement membrane seems to be very important in the pathogenises of diabetic retinopathy. There have been a lot of different factors suggested as to the cause of the diabetic retinopathy. The first factor that was thought to be the cause

for many years was that of hypertension. Hypertension lost
some of its popularity as the pathogenises after Ballantyne
and Loewenstein's[3] work in 1943 on the pathology of diabetic
retinopathy. Since that time, there have been many factors
suggested. Some of them more common ones have been: hyperlypemia.
Finley[12] has noted that the chylomicron levels are abnormally
high in diabetics and that they can be lowered by hepariniza-
tion. He is now working on these findings.

Cogan[9] has been doing some work on blood viscosity and
excessive hexosamine blood levels. These are abnormal in
diabetics but they are also abnormal in some other disease that
do not have any retinopathy. There has been a fair amount of work
done on pituitary adrenal hyperactivity. Oosterhuis[23] studied
the twenty-four urinary seventeen hydroxycorticoid excreation
for five consecutive days. On the third day he stimulated the
adrenal cortex with a six hour IV infusion of twenty units of ACTH.

He got no remarkable difference between the two groups
of diabetics with and without retinopathy. There was no difference
between the excreation before and after ACTH. This agrees with
other studies also. He also tried treatment of diabetic
retinopathy by subtotal adrenalectormy[24] after the subtotal
adrenalectory, he noted a reduction in the introcular pressure
to normal and an improvement of the retinopathy. In some if
there had been much new vessel formation after the subtotal adrenal-
ectomy, the scar formation would lead to detachment of the
retina. There was a marked reduction in the number of retinal
hemorrhages. Oosterhuis states that adrenalectomy is of only
doubtful theraputic influence.

Hausler[15] was able to produce microaneurysms in the retinas of metahypophyseal diabetic Chinese hamsters. The hamsters were produced by giving them 12.5 mg of cortisone and 4.0 mg growth hormone for ten days. The eyes were then examined. One of the microaneurysms found was from a capillary and one was from an arteriole. Contreras[11] tried to treat advancing diabetic retinopathy by hypophyseal stalk section. He tried it on eight patients who had had diabetes for fifteen years or more. After hypophyseal stalk section, the abnormal vascular pattern of the retina was the first element to be effected. The engorgement and dilatation was the first affected as these vessels returned to normal. Some of the neovascularization disappeared and was replaced by whitish fibrous strands. There was a marked attenuation of hemorrhagic activity. The micro-aneurysms with punctate hemorrhage tended to disappear. Contreras suggests that there is something important in the pathogenesis of retinopathy that has its origin in the hypo-phseal or hypothalamic region. This factor is probably important in the changes in the retinal and uveal blood flow which is caused by a change in the vessel tissue and vessel intraocular. fluid exchange.

Berken[4] worked on the ocular changes in the Shwartzman reaction. He noted retinal changes including deposition of PAS positive material within veins. With dilatation of these vessels and thickening of small vessel walls, he found aneurysmal capillary dilatation in one-third of the cases. The reaction that he and Adams[1] think is the factor, is that of intra-

vascular precipitation of a lipoprotein acidic polymer complex in the presence of a depression of the reticuloendothelial system phagocytic function.

Cogan[8] has put forth the theory that the capillary shunts were important in the pathogensis of the diabetic retinopathy. His theory is that after the capillaries loose their mural cells, the capillary with the least resistance will become distended. Then they become tortuous, kinked and highly cellular. The distended vessels will then develop saccular thickening and aneurysms. He thinks that this is a reaction to attempts to repair the capillary to normal. The shunts seem to always come from areterioles that come off as side arm branches from the main retinal artery. The shunt vessels arising from such would then replace a large vascular bed and be subject to relatively high intravascular pressure.

Wolters[29] has dealt with the intravascular mesodermal structures and has tried to show that areas on capillaries with insertion of the mesodermal strands can develop microaneurysms when the pull from strands causes the vessel to become kinked. The pull of the intravascular strands may be caused by the swelling of the retina. As stated by Ashton in personal communications with Wolters[30] he has also shown that in retinoblastomas there are many saccular microaneurysms much like those seen in diabetics with most of them being at the sites of fibrous strands insertion.

Pope[25] has postulated the theory of fat accumulating in the capillary wall with subsequent stretching of the wall so that there is a herniation through the supporting reticulium.

This then forms a minute aneurysm. The fat is absorbed into the capillary wall as serum lipids or as an embolus. The basement membrane is distended beyond the reticular supply, so there is a weakened spot in the wall which then herniates. The lipids are the PAS positive material that is found in the aneurysms.

The theory put forth by Leopold[18] was very interesting to me. This was that patients with a retinopathy that was considered typical for diabetes would give a normal response to a carbohydrate loading test but some may years later show or develop an abnormal glucose tolerance curves.

Of all of the theories given above, none of them have been able to give much information about the early microscopic changes of the capillaries. In 1961, Cogan[10] stated that there was no clear understanding as to why only the eyes and kidneys showed any vessel changes, but now with the electron microscope it has been shown that the vessels in other body tissue are affected. Bloodworth[5] has found changes in the basement membrane of the glomerulus, and the capillaries of retina and muscles but not in the subcutaneous capillaries. In the muscle capillaries, he found an increase in the mean width of the basement membrane but the mean width of capillaries found in fatty tissue were normal.

Bojser-Moller[6] has shown that skin capillaries had walls thickened up to ten times normal. This was due to peri-endothelial material which is PAS positive. He found that this is a diffuse capillary disease and not just of the eyes and kidneys.

As the author has shown above, there have been many theories put forward as to the pathogensis of the diabetic retinopathy but none have proven to be the exact cause. A good many of the theories seem to deal more with the cause of some of the secondary findings rather than the primary findings. I think the fact that the electron microscopy has now shown the early changes in the basement membrane and the early loss of the mural cell in diabetics much has been done to change the thinking as to the pathogensis of the retinopathy. Also with the electron microscope, it has been found in the kidney biopsy that there has been seen thickening of the basement membrane long before any functional abnormality is present. A similar abnormality has been found in the capillaries of the ear lobe in pre-diabetics.

Camerini Davalos[6] has stated a study with "pre-diabetics," that is patients who have a family history of diabetes but they themself show no abnormalities in carbohydrate metabolism.[6] He has found that the "pre-diabetics" have an increase in the venule-arteriole ratio in the conjunction, the normal ratio is 2.29 where as the pre-diabetics have a ratio of 4.22. One of the most striking findings is the change in the dermal capillaries from the ear lobe. The pre-diabetics dermal capillaries were commonly found to be constricted in relation to the normal capillaries. It was not in the venules that there was a mild degree of endothelial cell separation as well as an expansion of the potential space between the basement membrane and the endothelial cells. Both of these findings are within the range of physiologial variation but their constancy amoung this

particular group of subjects suggest a vascular lability not present in normal controls. He also noted that the vascular elastic tissue was considerably more dense and on occasion a fine fibrillar structures was visible. The kidneys also showed the irregular thickening of PAS standing material in the renal glomerular basement membrane and in Bowman capsule.

He has also found a substance in the serum he calls insulin-like activity which in normal people is 83 micro-units per milliliter and in pre-diabetics it is 203 micro-units per milliliter. What this substance is and where it comes from is not known as of yet but this may hold some of the answers of diabetes. He is still doing work on these patients and he plans to follow them for sometime to see how many will develop diabetes.

From the above, we see that the retinopathy has its start at the very beginning of the disease. The author feels that to find the true pathogensis for the microaneurysms a person will have to start at this "pre-diabetic" stage. For changes to have taken place so early in the disease, it seems almost as though there has to be a metabolic cause. However, this cause may be any where from adrenal hyperfunction, hyperinsulinism that most pre-diabetics have or hyperpitutary function. There is still much work that needs to be done in this area and as better methods are developed, I am sure the exact cause will be found.

III. Conclusion

1. Ophthalmoscopic changes in diabetic retinopathy are: microaneurysms, small round hemorrhages, dilated veins, waxy hard exudates, cotton wool patches and later large vitreous hemorrhages.

2. Electron microscopic changes are: thickening of the basement membrane of the capillaries, a marked decrease in the ramification of the mural cells, later a loss of the mural cells and their nuclei with a pale staining outpouching of the capillary wall-called ghosts mural cells, and proliferation of the endothelial cells. Then the microaneurysms are formed from these capillaries that have lost their mural cells. These thin walled microaneurysms later become thick walled hyalinized aneurysms.

3. Pathogenses of the retinopathy is still in question. Some of the hypotheses are hypertension, hyperlypemia, increased blood viscosity, pituitary adrenal hyperactivity, Shwartzman type of reaction, capillary shunts, intravascular mesodermal strands and fat accumulating in the capillary wall. The one that looks the most promising at this time is that of increased insulin-like activity found in the serum of pre-diabetics by Camerini Davalos. He also found the early basement membrane changes in capillaries in these same pre-diabetics. This pre-diabetic state seems to be where the first vessel changes occurs. The cause of these vessel changes seems to be corollated with the elevated serum insulin-like activity. This is the area that further work should prove to be very helpful for better understanding of this disease in the future.

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