8

THE PATHOGENESIS OF GLAUCOMA IN DIABETES MELLITUS.

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The ordinary eye affections occurring as complications of Diabetes mellitus are well known. It is unnecessary even to mention them. Glaucoma certainly does not belong to the commoner sequelae of this disease. Indeed, if diabetes be a cause at all, it must be rare, for how often do cases of glaucoma turn up at the larger cliniques and when it comes to a question of operation and the urine is examined, there is the usual note in the corner, Urine specific gravity .... acid or alkaline, no albumen, no sugar.

The object of this paper is to investigate and determine if possible, whether there is any question of cause and effect, whether glaucoma ever does occur as an affection of the eye, directly or indirectly traceable to diabetes.

On the whole, the evidence to be produced below, seems to be in favour of an answer in the affirmative, perhaps not so much as a direct consequence, but after an intermediate stage of diabetic hemorrhages. Of course it is plain enough to see the relation between iritis with subsequent posterior synechiae or an enlarged cataractous lens and subsequent glaucoma, but this

has

has been previously worked out and any iritis or swelling lens may cause this, hence also diabetic iritis and cataract. Apart from these undisputed and long accepted relations, however, I wish to submit a few cases having a different causal connection.

My interest in this subject was aroused by a case of glaucoma in a diabetic coming to Mr. Parson's clinique in the Royal London Ophthalmic Hospital - Moorfields. The patient had a painful, blind glaucomatous eye, but on account of his diabetes, the eye was not excised. This induced me to look up the pathological records at Moorfields where I found that during the last ten years, only four glaucomatous eyes had been excised in diabetic cases. Next I looked up the literature upon this subject and was astonished to find that it had apparently received but scant attention as is shown by the almost entire absence of references with any bearing on the point. Thereupon I decided to investigate this subject and through the kindness of Mr. Greeves, the Curator, I was allowed to make use of the above-mentioned pathological material.

The number four seems extremely small for a hospital, drawing from such a large community and possessing such a large In-patient Department. But when we consider how loath any surgeon is to operate on a diabetic when the anaesthetic is to be general, we have a ready enough explanation of the small number of cases which actually reach the pathology department of an

eye

eye hospital. Still more so, should the eye condition stand in some possible, even though obscure relation to the systemic disease, for most complications of diabetes whether in the eye or otherwise, are generally considered as warnings if not actual danger signals. Hence we may safely conclude that though blind and painful eyes are seldom excised in diabetics, the condition itself and the sequence of ocular trouble preceding it, is by no means so rare as the above number would seem to indicate.

As a starting-point then, I wish to submit these four cases from the Royal London Ophthalmic Hospital, followed out, as far as possible, from beginning to end, i.e. the time of patient first presenting himself for examination until the final end of that particular eye, excision and pathological section. In addition, I shall give the clinical history of the case which first aroused my interest in the subject, and the eye of which I was most anxious to obtain for pathological section, but the surgeon under whose care the case was, rightly refused to excise it on account of the danger involved in general narcosis. The eye was the more interesting as there was a history of having used drops for some time and the question of atropin causing or precipitating the attack of glaucoma might have been discussed or even proved or disproved by the microscopic appearances.

CASE I. E.B., a woman aged fifty-one, first came to consult Mr. Arnold Lawson in October 1909. She was then suffering from

failure

failure of vision in both eyes. Ophthalmoscopically the picture was that of hemorrhages of the retina and there being sugar in the urine 3.3% but no albumen, the diagnosis of "diabetic hemorrhagic retinitis" was accordingly made.

On April 2, 1913, she was suffering from iritis in the left eye, which she stated had been "inflamed" for one week. She was directed to use one half per cent. atropin drops three times a day and to report herself in a few days. But it was not till three weeks later, that she turned up again, having been prevented from attending through the illness of her husband. The pupil was dilated, tension ±1, but went down immediately with the application of eserine. She was however, admitted and seeing that myotics were not keeping the tension down, a paracentesis was done on the left eye on May 9, 1913, followed by Herbert's sclerotomy on May 14, 1913.

Three months later, she was again admitted for the left eye. The <u>right</u> she could not complain of! There was no injection anywhere, it had a bright cornea, a good anterior chamber and active pupil. However, there was only a dull fundus reflex, not permitting any details to be seen. The tension was normal.

The <u>left</u> eye was injected though the conjunctiva was clean, the cornea was dull and the anterior chamber contained a large hyphaema. The iris was muddy, the pupil semi-dilated

and

and inactive, and a very dull reflex was obtained from the fundus, so much so as to suggest a hemorrhage into the vitreous. The tension was now +1 and vision reduced to the barest perception of light.

Next day, August 16, 1913, Elliott's trephine operation was done which left a large filtering scar a few days later, but the hyphaema in the anterior chamber persisted.

A week later, filtration was not so good, the anterior chamber was deeper than before, but the hyphaema persisted. There was much ectropion of the uvea, but a good fundus reflex, the tension was again raised to +1.

On September 2, 1913, the left eye was excised.

On leaving the hospital, the vision of the right eye, corrected by glasses, was $6/36$, she has since been under observation and the sight of this eye is now (Jan. 14, 1914) reduced to $2/60$, which is not improved by glasses and I suggest that the second eye is going exactly as the first did.

But to return to the excised eye.

This was fixed in Zenker's solution, washed, frozen, cut in vertical section, passed through alcohol and iodine, and soaked in celloidin. The appearances showed a shallow anterior chamber with occluded angles, hemorrhages in the vitreous and numerous retinal hemorrhages, all the coats were however, in situ.

Sagittal

Sagittal Microscopical sections of the whole eye were then made the optic nerve having previously been cut out and set aside for separate serial section. The conjunctiva was oedematous in the neighbourhood of the trephine wound. The iris was adherent to the cornea peripherally to somewhat beyond the commencement of Descemet's membrane. There was sclerosis and atrophy of the iris, with marked ectropion uveae and a vascular membrane on the anterior surface of the iris. Its posterior pigment layer showed oedema for almost the whole length of the iris. The tissues of the ligamentum pectinatum were condensed showing fewer endothelial cells than normal. The ciliary body was atrophic, and the lens is not pushed forward up against the iris.

There is much thickening of the retinal arteries, with plenty of hemorrhages into the substance of the retina, the inner layers of which are atrophied. There is recent hemorrhage into the vitreous at the papilla.

The choroidal vessels show general thickening of the arterial walls whereas the veins are normal. The nerve was separately mounted and cut in series in coronal section, i.e. perpendicular to the direction of the vessels and nerve fibres (every third section being mounted and stained) and a special examination made of the vessels and their walls. The nerve tissue itself was atrophic.

At

At the papilla, recent hemorrhage into the vitreous was abundantly visible, passing backwards from this section an anterial branch with much thickened wall and a small lumen is seen. The artery itself is seen in the next section whereas a branch of the vein is cut longitudinally. Similarly in the next until there is only the main vein and artery seen cut transversely.

The branches are thick-walled, but the artery itself shows such an increasing amount of subendothelial thickening that in the 24th section, the lumen though still present could barely hold one red blood corpuscle, and the subendothelial tissue takes up about five-sixths of the whole thickness of the artery wall.

Meanwhile the vein has developed a thrombus which extends from the 12th to the 30th section, but still leaves the lumen half its cross-section area. The lumen persistently diminishes from the place where the thrombus stops until in the 60th section,it reaches its minimum, 4 red blood corpuscle diameters, but this is by a uniform thickening of the wall, a periphlebitis. After this, the vein lumen increases, receiving tributaries and though at sections 114, another branch is seen entering it and at 129 there is again increasing periphlebitis, the vein shows nothing further of interest.

The

The artery lumen as before-mentioned, is for all practical purposes occuluded at section 24. For 18 sections it cannot hold more than 2 or 3 red blood corpuscles, then slowly increases in size until at section 72 its lumen occupies about one-third of its area of cross-section. After this, the artery increases a little more in parts, but there is nothing of further interest in following it up.

Altogether 180 sections were cut, but though they commenced beyond the retinal end of the central artery, they did not reach the proximal or cranial end of the artery and vein, the nerve not having been cut long enough in the original excision operation.

The condition of the retinal vessels then was one of extensive and irregular disease. The central artery was practically occluded at one place, and its retinal branches irregularly thickened. The central vein was not much more patent though its minimum lumen still had a diameter of 4 red blood corpuscles. Apart from the afore-mentioned thrombus it and its retinal tributaries show evidence of much periphlebitis.

This completes the microscopic findings in Case I.

CASE II. A man aet. 66 came under the care of Mr. Lawford on April 26, 1905. He had consulted Mr. Tweedy a fortnight previously who is said to have reported the condition of the left

eye

eyeas "obscure and serious"; the patient states that the eye had become "red and watery" three weeks before that and had given him considerable pain at times. He also states that he was suffering from diabetes for the last two years. On examp ination of the left eye, this showed a discoloured iris, a shallow anterior chamber, only a dim light reflex with no view of the fundus. Tension was high + 2.

The right eye was apparently normal, having a clear bright cornea and iris, small active pupil, normal fundus and vision of $6/_6$; tension normal.

There was no albumen in the urine which however, gave a well-marked reaction to the sugar tests.

This was again examined on April 29, 1905 with the same result. By now he complained of a moderate degree of pain.

After treatment with eserine failed, he was admitted to hospital and on May 13, 1905, the left eye was excised. By that time it had developed bullous keratitis. The cornea was hazy, there was much ciliary and conjunctival congestion, the anterior chamber was more shallow, the pupil was dilated eccentric and inactive, the iris was dull. No view could be obtained of the fundus but he still had $4/_{60}$ vision and his light projection was both correct and rapid. The tension was still + 2 . The excised eye was now subjected to exactly the same process as in Case I, but <u>horizontal sections</u> were made of the globe.

The

The corneal epithelium is partly lost, the anterior chamber is of good depth, but the iris is applied to the back of the cornea at the angles. The lens is in situ and almost fills the interciliary space. The vitreous contains a little blood below. The retina is in situ, but studded with punctate and mostly round hemorrhages of small size; there are no white spots.

From the lower part of the disc, a membrane stretches for about 1-1½ mm. into the vitreous, in which it ends by two pointed processes which go off temporally and nasally respectively. There are a few small vessels connected with the central vessels, entering its base and it stretches for a little way beyond the disc along an inferior temporal vessel. There is some hemorrhage lying just beyond its end in the vitreous. The disc is little if at all cupped.

Microscopical Section.

The corneal epithelium is lost in places, the stroma is normal. The corneo-iridic angle is blocked on both sides about as far forward as the end of the membrane of Descemet. There is a vascular membrane on the iris, the stroma of the latter is condensed and cellular, but without any localised round cell infiltration. There are no diabetic changes in the pigment epithelium. The anterior lens capsule shows a little pigment. The ciliary

body

body and choroid are normal.

The retina is for the most part normal. In places there is considerable atrophy of the inner layers especially the nerve fibre and ganglion cell layers. There is a considerable number of hemorrhages but they are all small, most are in the inner layers, but a few penetrate to the outer and some even into the sub-retinal space. There is vascular disease of very irregular distribution, many vessels being quite normal while close to them thickened vessels are found. Some of the smaller peripheral arteries show marked degeneration with complete obliteration of their lumina. The process is generally one of fibrosis rather than one of endothelial proliferation. In places there is a little convoluted almost capillary lumen (probably of a vein) with a few blood corpuscles in it, and surrounded by a large, very pale area with scanty oval nuclei; the lumen is lined by a single layer of endothelial cells. In the equatorial region over a small area, under a vessel, the inner layers of the retina are bowed out towards the vitreous and small cysts of hemorrhage are seen in the intergranular, the ganglion cell and the nerve fibre layers. There are ordinary cysts at the ora serrata as well, and near the fovea, a few coagula are seen in the intergranular layer.

The nerve was now cut in series as in Case I, and showed a very much distended vein on the disc which in passing through the

the lamina cribrosa suddenly becomes small and is encroached upon from one side by cellular connective tissue. The vein lumen also becomes divided into two by a delicate trabecula (of detached endothelium ?). The lumen is, however, patent throughout. Behind the lamina cribrosa, the vein lumen again becomes larger, but is still smaller than normal and the wall abnormally thick (fibrosis). The artery is widely patent and normal on the disc also in passing through the lamina cribrosa and behind it, in fact, it remains practically normal throughout. The nerve is considerably atrophied and shrunken.

CASE III. This might be considered a mixed case of diabetes and nephritis, but the diabetic changes in the pars iridica retinae are so well marked that the predominence of the diabetic intoxication is indisputable.

A. B., a male aged 67, came under the care of Mr.Lawford giving the following history.

Seventeen years ago, he had received a blow on the right brow, but he did not consider that the sight of the right eye was any worse than that of the left for years after. But seven and a half years ago, he began to notice that the sight of the right eye was failing and on consultation was told the retina was "cracked". He could read a newspaper with the other eye (left), but cannot give an estimate of the amount of vision of the right. Meanwhile the sight of the better eye (left) has been

been steadily failing. One month ago, the bad eye (right) became "inflamed and red" and a week later, the pain began recurring at intervals. He had not vomited lately.

His general health had always been good and he complained of no symptoms of diabetes. His arteries were fair and the pulse perhaps suggestive of high tension, the knee-jerks were absent, the urine contained a fair quantity of albumen and sugar.

On examining the right eye, this presented much conjunctival and ciliary injection, there was localised oedema of the cornea in several bullae and the posterior surface showed rather coarse light brown punctate deposits. The anterior chamber was rather deep and the iris of a russet hue covered by a thick network of vessels on its surface. The pupil was more than semi-dilated, elongated and fixed. The lens showed an anterior linear and other indefinite interstitial opacity. There was the suggestion of a fundus reflex, vision was reduced to hand movements and the tension raised to +1. The left eye is interesting, its conjunctiva and cornea were normal and bright. The iris was of a similar hue as the right, but had a less pronounced prominence of vessels, chiefly around the pupilary margin. The pupil was likewise inactive to light and convergence, vision was $^{6}/_{60}$ only, which was accounted for chiefly by an irregular lens opacity. The disc was pale with small arteries and showed numerous hemorrhages near it, there was also a lustrous white exudate

in

in the course of the superior temporal vessels; the tension was normal. The bad eye (right) was promptly excised.

It was treated in the same manner as described in Cases I and II, but the section went right through the optic nerve so that this could not subsequently be cut transversely in serial section with the result that the minute changes in the central vein and artery could not be observed as in Cases I and II. But still the retinal arteries and vein are quite sufficient to give an idea whether or no there is any likelihood of the central artery and vein being diseased.

The eye was cut in horizontal section.

The corneal epithelium was stripping off in the area of the oedema mentioned in the clinical notes. The lens was found in situ, likewise the retina and the choroid. There are many small hemorrhages in the retina spreading in all directions near the disc, present, especially in the macula. The retinal vessels do not give the appearance of being enlarged, nor the disc of being swollen. Microscopically there is slight oedema of the corneal epithelium, the stroma however, is normal. The cornea-iridic angle is occluded to about half the extent of the ligamentum pectinatum, there is coagulum lying in the anterior chamber which shows a fibrous membrane on the anterior surface of the iris, especially well marked around its periphery. The iris stroma is somewhat condensed and hypercellular.

Diabetic

Diabetic changes are well marked in the pigment epithelium, to such an extent that there is a loosening and partial disappearance of this pigment with a tendency to heaping up of the remains in the cell walls. This condition affects both layers so that the dilatation is shown up well, in fact, the posterior layer is actually seen projecting in folds in places. This change is, however, not so marked near the sphincteric border, and ceases most abruptly at the root of the iris. Some small vessels are seen between these two layers. The ciliary body itself is slightly atrophic, and shows a few small round cell infiltrations in some fibrous tissue on it inner aspect. The choroid is quite normal. The lens shows some cataractous changes in the cortex.

Retinal changes are chiefly seen in the posterior part especially near the macula. Hemorrhages present here, are usually small and confined to the inner layers, but reach in places as far out as the outer nuclear layer. Between the nuclear layers, there are also coagula present, some of which have a homogeneous structure and are almost hyaline looking with nodular rounded outlines, others are granular and less definite in outline. In the macula, these spaces are especially large, some containing debris, some a fibrinous network and some being empty. The fovea is occupied by a congeries of such spaces. Where these spaces are present, the retinal elements are much scattered and distorted.

distorted. The rods and cones are usually present, but at the fovea the cones have lost their outer limbs. The outer nuclear layer suffers least but is thin and crushed up against the external limiting membrane. The inner nuclear layer is much scattered, especially in the macula. The ganglion cell and nerve fibre layers show a good deal of atrophy apart from prope diabetic changes. Vascular disease is present but irregular in distribution. A large artery on the papilla shows eccentric narrowing of the lumen from proliferation of its subendothelial layers. A macular artery shows great thickening of its wall with narrowing of the lumen, but many other vessels are normal. The papilla is of the myopic type, the nasal edge overhanging in a long spur, the temporal side is more sloping, the pigment epithelium ceases some distance out within which point the retina is fused with the choroid. The nerve is atrophic.

CASE IV. No clinical notes of this case are available. The patient, a man, was a diabetic whose right eye was excised on the first occasion that he was seen by the surgeon, Mr. Percy Flemming. This eye was subjected to the same pathological treatment as the previous three cases, here too, the nerve was unavailable for serial section, having been previously cut in horizontal section, together with the whole globe.

The cornea shows bullae below, the anterior chamber is fairly deep, but the corneo-iridic angle is occluded. The lens is

is cataractous but in situ. There is much hemorrhage in the vitreous, also several broad fibrous bands stretching in various directions. A membrane stretches across in the region of the ora serrata. Among the strands, cholesterin and coagulum is seen. The posterior part of the ciliary body and the anterior portion of the choroid are slightly detached, leaving a subchoroidal coagulum.

Microscopical Section.

There is some spreading in of the cellular tissue between the corneal epithelium and Bowman's membrane. Otherwise the cornea is normal. The corneo-iridic angle is occluded on both sides by adhesion of the iris. The iris stroma itself is condensed and atrophic, and considerably infiltrated with patches of lymphocytes in places. A fibrous membrane is present over the anterior surface. Between the iris and the lens, and around the equator of the latter, there is a considerable quantity of cellular tissue. In the lens itself, there are considerable deposits of anterior capsular cataract and breaking down of the cortex. The ciliary body is atrophic and somewhat infiltrated. The posterior part of the ciliary body and the anterior part of the choroid are slightly detached, leaving a subchoroidal coagulum as mentioned in the macroscopic section. The choroid is very considerably infiltrated, especially anteriorly and about the equator. Posteriorly, there is less recent infiltration,

but

but the choroidal structure is much destroyed, its stroma is condensed and fibrous, the vessels have disappeared and the suprachoroidal space is obliterated. Plaques of bone are actually present near the nerve entrance.

The retina is detached from the ora serrata to the disc. It is very greatly degenerated and full of large cystic spaces containing sometimes blood, sometimes coagulum. In the subretinal space, there is abundant blood which is undergoing organisation apparently from the choroid. On the surface of the choroid, the process is most advanced, the pigment epithelium is destroyed, a layer of very dense, slightly vascular fibrous tissue is seen on the surface with occasional adhesions to the choroid where the membrane of Bruch is broken through. In places, the tissue is more cellular and recent blood and cholesterin crystals spaces are present among it. Towards the centre of the globe, the hemorrhage is more recent and unaltered, but some strands of slightly organised cellular tissue run through it in various directions. The nerve is atrophic and very cellular. There is some organisation also on the anterior surface of the retina, its blood-vessels are throughout very difficult to identify on account of the quantity of hemorrhage almost all over the section, but what can be seen of them is extensively diseased

CASE V. S. G., a Jew, aged 55, came to Mr. Parson's clinique on January 21, 1914, suffering from acute glaucoma in the right eye.

He

He had had "neuritis" and was treated for this in the country. The right eye first became painful about the end of November of last year although he had seen haloes round lights three months previously. About the end of December, he was treated with atropin and dionin.

On examination, the right eye presented the usual symptoms of glaucoma, ciliary injection, hazy cornea, shallow anterior chamber semi-dilated immobile pupil, tension + 2, with no perception of light.

The left eye was practically a normal eye, tension normal, no cupping although the fundus was difficult to see, vision was $6/_6$ with his correction. There was much sugar in the urine. He was treated with myotics leeches and hot bathing. The pain diminished, but he was still very sorry for himself when he left the hospital on February 2, 1914, Mr. Parsons refusing to excise the eye or do any operation whatever. Since then, he has been to the out-patient department, but I have been unable to follow the course of this case any further.

The literature upon the subject as I have already mentioned, is exceedingly small.

The

The Text books of Ophthalmology do not mention glaucoma as a complication of diabetes at all. Fuchs does not say a word about it in his classical work.

De Schweinitz does not consider it in his "Diseases of the Eye" and even in the larger reference works such as Parsons' "Pathology of the Eye" and Graefe-Saemisch's "Handbuch der gesammten Augenheilkunde"; what mention there is made of it, is indirect.

True enough, Schmidt-Rimpler in Graefe-Saemisch (1) makes the definite statement that "diabetes is not a direct cause of glaucoma, but it exercises probably a sufficiently unfavourable effect upon an ordinary intercurrent glaucoma".

So it does, on practically any intercurrent disease, ocular or otherwise, in fact, the above statement hardly brings us any nearer to the truth.

Parsons (2) does not refer to it directly in his complications of diabetes, but in diabetic retinitis, he mentions "thrombosis of the central vein, embolism of the central artery and hemorrhagic glaucoma".

Knapp (3) mentions a case where the patient suffered from diabetes and obstruction of the central artery occurred in one eye only, which later developed hemorrhagic iridochoroiditis, and glaucoma followed probably as a consequence.

Leber (4) gives a case of a diabetic with evidence of syphilitic disease, who also suffered from hemoptysis and liver trouble, in whom slight albuminuria replaced the previous glycosuria.

The

The general condition was thought to be hypertrophic hepatic cribosis. There were few prodromata and blindness of one eye resulted after vitreous hemorrhages and later "serous iritis becoming the glaucomatous state". A few months later, while under observation, "hemorrhagic retinitis" developed in the other eye, later still a pericarditis. Even this second eye was lost through iritis and glaucomatous inflammation in spite of sclerotomy.

(5)
Hirschberg mentions a case of a patient of 66, with diplopia on account of a right abductor paralysis. Patient also had an incipient cataract, developed facial paralysis next year and had the left foot amputated two years later for gangrene. There was very little sugar, but albuminuria. Next year, the right eye developed "hemorrhagic retinitis" becoming hemorrhagic glaucoma; soon after this, a severe hemiplegia of the left side followed.

(6)
Coats gives a case in great detail, of which the chief clinical points are as follows:-

A gentleman, aged 65, complained of gradual failure of vision in both eyes for some months. In October 1904, right vision suddenly diminished and patient presented himself for examination. Right vision was $6/_{24}$, the pupils active, the tension normal and the media clear. On ophthalmoscopic examination, the superior temporal artery was found to be narrowed and the blood stream within it was interrupted and showed the characteristic breaking-up of the blood column. The circulation of this artery was distinctly visible in its normal direction and ceased altogether with the slightest pressure on the globe. The other

branches

branches of the retinal artery, beyond showing some thickening of the vessel wall, as evidenced by damming of the venous blood-stream, where crossed by the arteries, were normal. The veins were normal. Around the macula, there were numerous small white retinal patches and scattered throughout the fundus, several small striate hemorrhages. Examination of the field of vision showed an absolute sector-shaped defect down and in, corresponding to the block in the superior temporal artery. In the left eye, the vision was also reduced to $6/_{36}$. Tn, pupil was active, media clear. Ophthalmoscopic examination showed retinal changes similar to the right, but rather more marked. The arteries presented some sclerosis but were otherwise normal; the veins were normal, the field of vision was full. The urine was of high specific gravity and contained much sugar, but no albumen. The heart and lungs were normal. Late in November 1904, sudden violent pain set in in the right eye with vomiting. The patient was seen two days later, when the right eye presented all the signs of an acute glaucoma, with T +3 and no perception of light. The eye was therefore enucleated next day. The eye and nerve were each cut in serial section.

Briefly summarised, the pathological changes found were as follows:- Hemorrhages in the anterior chamber which was deep, hemorrhages also in the iris stroma, anterior portion of the ciliary body and spaces of Fontana. Moderate adhesion of the

root

root of the iris to the back of the cornea without much condensation or atrophy. Vacuolation and loosening of the pigment epithelium strictly confined to the iris and not encroaching at all on the ciliary body. Hemorrhages and exudative patches in the retina. Narrowing of the lumen of many of the retinal arteries by endothelial proliferation, amounting to complete blocking in the case of the superior temporal. In the main stem at the level of the lamina cribrosa, a localised nodule of endarteritis almost fills the vessel, but leaves a narrow lumen at one side. Further up the nerve, the artery is free for a space and then again much narrowed by endarteritis. The vein is cavernous within the lamina cribrosa; farther up the nerve, it is small with round cell infiltration of its well, then becomes normal again in size and appearance.

I have quoted this case rather more fully as it is the only one I could find in which a full pathological examination in serial section had been made both of the globe and the nerve, in an undisputably diabetic case. Alvarado (7) wrote a monograph in one of the Spanish-American journals, questioning the existence of iritis and glaucoma in and by reason of diabetes. He also asks whether it is legitimate to perform iridectomy in such glaucomatous cases. It is a great pity that I could not get access to this paper, I very much question whether it is to be found in any of the libraries in London, certainly I did not

succeed

indeed in doing so. The contents of such an article might have had a bearing of supreme importance upon my results, but as I could find no further reference to it or its contents, it is perhaps reasonable to suppose that it covered old ground and did not add anything to the knowledge of the pathogenesis of glaucoma in diabetes. Moskowitz (8) published a case which seems an almost direct and affirmative answer to Alvarado's questions. An insurance agent, single, aged 64, came up for examination in May 1909. Vision had been failing for eighteen months in the right eye and was now reduced to perception of light. This eye never improved again and no further mention is made of it. The left eye is the important one, it had vision of fingers at one foot only and tension + 1, the cornea was clear, the pupil acted to light sluggishly, the fundus showed no cupping of the disc. There was no personal or family history of importance. The urine contained sugar only. With dieting and myotics, vision improved to $20/_{80}$, in a fortnight, an iridectomy was then done and a month after operation, vision was $20/_{30}$ partly, when corrected with the right sphere -2. On discharging the patient, he took to his old diet and habits again, his vision was reduced to $20/_{70}$ in three weeks and he was ultimately sent to a general hospital for anti-diabetic treatment and to regulate his loose habits.

Moskowitz then in discussing the case, dismisses all other possible predisposing causes of the glaucoma, such as hypermetropia, for the patient was myopic, sex and race for he was a male

and

and a German, not a Jew. Neither was there any hereditary predisposition to glaucoma and by a process of exclusion, and perhaps still more by his therapeutic results, diabetes becomes the causal factor. Regarding the good progress of the eye before and after operation, one wonders how much of this is due to the iridectomy and myotics and how much to dietetic treatment, its later behaviour and the condition of the other eye, rather suggests that after all, it will also fall into line with the other cases mentioned in my paper.

So far the case is recorded, and on the whole, seems to be quite different from the others. But the details given, are not exact enough, no mention is made of the presence or absence of hemorrhages anywhere, in the retina or vitreous, whether there was any retinitis at all. Indeed, a fundus in an eye with such poor sight, is during an acute attack, very difficult to see to investigate such "minor clinical points" which for the purposes of this paper, however, are most important. And as the case is a purely clinical one, it is only valuable as an example of glaucoma occurring in a patient with diabetes.

Let us sum up the important points of the various cases mentioned and in doing so, leave those cases to the last, of which pathological examinations were made as they require fuller discussion.

Knapps case commenced as an obstruction of the central

artery

artery of the retina, later hemorrhages and glaucoma.

Leber's case can hardly be considered a diabetic at all. The patient suffered from a multitude of things, amongst which certainly vascular disease must take a prominent part and both eyes developed glaucoma after hemorrhages.

Hirschberg's case also is more likely of albuminuric than glycosuric origin. Here too though, hemorrhagic retinitis precedes glaucoma.

Case V. looks like an intercurrent glaucoma precipitated by atropin, though pathological examination might have disproved this by noting the condition and relative position of the ciliary processes lens and iris, etc.

To come to those of which microscopic sections were made.

Coats case was undoubtedly a pure diabetic for there was no albuminuria, the heart and lungs too, were normal. There was gradual failure of vision associated with vascular thickening in the left eye. Sudden diminution of sight in the right eye followed some two months later by acute glaucoma, and excision. Pathologically the anterior chamber was deep, showing hemorrhage, the iris ciliary body and spaces of Fontana showed hemorrhages and the root of the iris was adherent to the back of the cornea. The retina and central vessels showed extensive vascular disease hemorrhages and exudates.

Case

Case I had diabetic hemorrhagic retinitis four years previously. Paracentesis and sclerotomy were tried, trephine three months later, but the eye had to be excised ultimately.

Pathologically, a shallow anterior chamber occluded angles, vascular membrane on anterior surface of iris, vitreous hemorrhages.

Retinal vessels extensively diseased, central vessels showed endarteritis and periphlebitis as well as a thrombus.

Case II, a serious and obscure case a fortnight ago. Excision one month later. Pathologically, a normal anterior chamber corneo-iridic angles blocked, vascular membrane on iris, vitreous hemorrhages, considerable number of small retinal hemorrhages, vascular disease of irregular distribution, central artery of retina widely patent throughout, central vein distended on disc small in passing through lamina cribrosa, but likewise patent throughout.

Albumen doubtful, sugar certain.

Case III. Blow on right brow seventeen years ago, ten years later, sight began to fail "Retina cracked".

Three weeks ago, inflammation with punctate deposits and a deep anterior chamber, vascular membrane on iris. Other eye $6/_{60}$ vision and numerous hemorrhages near optic disc. Albumen and sugar. Pathologically numerous small retinal hemorrhages, vascular disease of retinal vessels present though irregular in distribution. Deep anterior chamber occluded cornae iridic angles and vascular membrane on anterior surface of iris,

no

no vitreous hemorrhages.

Case IV. No history. Sugar. Pathogically the whole eye is almost all hemorrhages, vascular disease of retinal vessels. Fairly deep anterior chamber, occluded corneo-iridic angles, fibrous membrane on anterior surface of iris, vitreous full of new and old hemorrhages.

Now all these four cases had hemorrhages, all had diseased retinal vessels, all had a vascular membrane on the anterior surface of the iris producing partial ectropion uveae and all had dense peripheral adhesions of the root of the iris to the cornea.

Such then are the cases examined pathologically together with such others as I could find in the literature of which I have made a careful search.. Of these, Coats' case is the only one of which a pathological description was available, it was probably the only one so examined, and it has in common with the above four, the diseased vessels,hemorrhages and adhesion of the periphery of the iris to the cornea.

The conclusion seems irr~esistible. Here are five (including Coats' case) pathologically examined eyes, the only ones in which glaucoma and diabetes were associated and in certain outstanding pathological features, they all agree. Are we to suppose that this glaucoma is merely a coincidence, i.e. a senile glaucoma occurring in a diabetic person; a likely enough occurrence.

The

The answer is that the type of glaucoma is not senile, the lens is not forward, there is no swelling of the ciliary processes, in fact, rather the reverse is the case, they are normal or atrophied. The type of glaucoma is indeed such as is invariably assosiated with intraocular hemorrhages, and has been shown by Coats to be especially associated with thrombosis of the central vein.

With regard to the explanation of this glaucoma, the theory has been advanced by Tatsuji Inouye, (9) working under Coats, that the glaucoma is secondary to the hemorrhages in the retina which are produced by the venous thrombosis. To quote Inouye's own words:-

"The obstruction causes retinal hemorrhage; the blood corpuscles in disintegrating produce toxines; the toxines are continually carried to the angle of the anterior chamber, owing to defective drainage by the central vein and its collaterals; the tissues about the angle become inflamed, an adhesion is formed and glaucoma is the result."

Now all the above five cases had retinal hemorrhages, therefore it is reasonable to suppose that glaucoma in diabetes, apart from such as is caused by diabetic iritis or cataract, may be secondary to these retinal hemorrhages.

But where do these hemorrhages arise? Why should there be any at all? What has diabetes to do with hemorrhage? The

association

association of retinal hemorrhages with diabetes is well-known clinically and the occurrence of arteriosclerosis has also been abundantly shown, both clinically and pathologically. (Nettleship & Lawford,[10] Hummelscheim & Leber,[11] etc.) The eye is not the only situation in which the connection is manifest since arteriosclerosis is certainly a main factor in producing diabetic gangrene of the extremities.

Another point is the condition of the vessels.

Is venous thrombosis necessary or can the ordinary hemorrhages dependent on the diabetic condition alone produce glaucoma? Must such profuse hemorrhages as a thrombosis entails, be present or will the ordinary "Diabetic hemorrhagic retinitis" be sufficient? Evidently the latter is quite sufficient for in Cases II and III, small hemorrhages were present. In Case I and Coats' Case, obstruction of the central artery or a branch combined with more or less narrowing of the lumen of the vein, were found, in fact in Case I, a thrombus occurred in the vein, which did not however, narrow the lumen nearly so much as the condition of periphlebitis further along the course of the vein. The clinical cases quoted, seem to have shown profuse hemorrhages as in Case IV, except Moskowitz Case in which the record is incomplete.

Thus

Thus I submit that Diabetes causes vascular disease in the eye, which in turn gives rise to retinal hemorrhages and these to glaucoma. Such then is the pathogenesis of glaucoma in diabetes.

Venous thrombosis though an occasional complication, is not essential for the production of the condition.

In conclusion, I have to thank Mr. Lawford, Mr. Percy Flemming, Mr. Arnold Lawson and Mr. Parsons, for their kind permission to make use of these cases, and above all, Mr. Greeves for permission to work in his laboratory and for the generous encouragement so frequently and willingly given.

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SUMMARY.

Diabetes as a cause for glaucoma has practically not been investigated before as shown by the small number of references to it.

Four cases reached the Moorfields Pathological Laboratory during the last ten years, which figure is much below the actual number of cases occurring, as surgeons are extremely loath to excise eyes in diabetics.

Serial sections were made stained and mounted. All show the same changes, diseased retinal blood vessels, hemorrhages, etc., analogous to glaucoma after thrombosis of the central vein of the retina. This glaucoma is quite different from the ordinary senile type. Therefore it cannot be a coincidence an intercurrent glaucoma occurring in a diabetic.

Arteriosclerosis present in diabetes is the cause of the vascular change and hemorrhages, which in their turn, cause glaucoma.

Thrombosis of the central vein, although it may be present, is not an essential factor, the ordinary diabetic hemorrhages are sufficient.