A CASE OF GLYCOSURIC RETINITIS, WITH COMMENTS.

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The case I am about to communicate, illustrative of one of the ocular lesions associated with diabetes mellitus, may I hope prove of interest to ophthalmic surgeons. The case has a twofold value—clinical and pathological. It is valuable clinically, as diabetes was detected from ophthalmoscopic changes. It is valuable pathologically from the careful histological examination of the tissues of the eye by Mr. Nettleship; the cases being very few where a microscopic examination has been made, and but little being known as to the immediate cause of the retinal changes.

It may not be amiss if I preface the case by a brief review of what is known concerning glycosuric retinitis, as it will serve to direct attention to the most important points. In doing this I shall have to draw largely from Professor Leber's article, "Ueber die Erkrankungen des Auges bei Diabetes mellitus," which appeared in v. Graefe's Archives in 1875.* Professor Leber has collected eighteen cases of this disease, and added another, examined with great care and minuteness by himself.

Glycosuric retinitis rarely occurs until diabetes has been in existence for a rather prolonged period. It is generally ushered in by a more or less sudden and partial loss of sight, generally one eye suffers before the other, but in most cases the two eyes are eventually attacked, though often with unequal severity. Sometimes sparks are seen before the eye or eyes, at other times dark spots or muscæ are complained of, whilst in some cases disturb-

* V. Graefe's Archiv für Ophthalmalogie, Band xxi, Abth. 3.

ance of the perception of colours is noticed. Pain does not appear to be of common occurrence. Patients usually have a succession of attacks of disturbed and limited vision, and between the attacks the sight may be in a great measure restored. In some cases the vision is almost completely lost in one or both eyes. On ophthalmoscopic examination the lens is usually observed to be quite transparent. The optic disc is sometimes found red, sometimes atrophic. The retina is generally cloudy; the vessels in many cases are distended and dilated, but in others, especially as regards the arteries, are smaller than natural. Scattered over the retina are apoplectic spots. These sometimes occur as round patches of various size, from large blots to punctiform ecchymoses; sometimes as linear streaks occurring in the course of the vessels; again at other times, as linear streaks running in a direction at right angles to the vessels. Sometimes the hæmorrhages are beneath the superficial layers of the retina, when the retinal vessels may be observed crossing the extravasation; at other times the hæmorrhages are superficial, and obscure the vessels. The hæmorrhages vary in tint according to their age. They often have a brownish-red hue. In addition to the hæmorrhages, white spots are seen scattered over the fundus. They are of various sizes and shapes. Sometimes they are of opaque whiteness, at other times they have a glistening appearance: those having the last character being generally smaller, and arranged in constellations. Such constellations are found grouped around the yellow spot, but are not limited to this situation. Occasionally longish white raised patches or folds, surmounted by retinal vessels, are seen. Some of the white patches are, doubtless, altered extravasations, for white patches are met with having red borders. Others would appear to be due to fatty degeneration of the retina. Though these appearances are seen with more or less clearness in most cases at some period of the disease, yet in other cases the details of the fundus are obscured by

opacities in the vitreous. Sometimes on examination nothing can be seen but a red reflex; sometimes floating films can be detected, having a red or brownish colour; at other times the vitreous is simply turbid and cloudy. These opacities of the vitreous are obviously due to hæmorrhages. They are found to occur coincidently with sudden limitations of the visual field, and they may be observed undergoing absorption.

The appearances in the retina are very like those met with in connection with Bright's disease. So close is the resemblance that some observers have passed them over as albuminuric changes, indicative of nephritis brought about by the diabetes. This opinion is favoured by the undoubted co-existence of albuminuria with glycosuria in the majority of the cases. Besides the presence of albumen, casts and blood have been found in the urine of some patients, who have, moreover, presented other evidences of Bright's disease, such as dropsy, hypertrophy of the heart, &c. Still, there remain a certain number of cases where it is expressly stated on competent authority, that there was no albuminuria. Thus in two cases recorded by Desmarres,* one by Noyes,† and one by Haltenhoff,‡ there was no albumen in the urine; in some of the cases the urine was examined repeatedly with care. In Noyes' case the amount of urea was on several occasions estimated and never found deficient. It thus seems clear that the changes are not necessarily of an albuminuric origin. In some of the cases the sugar had been noticed to almost or entirely disappear before the retinal affection was observed. What seems further to distinguish the intraocular changes in glycosuria from those met with in Bright's disease is the frequent complication of the former with

* Traité théor. et pract. des mal. des yeux. 2nd ed. Paris, 1858, t. iii, pp. 521—526.

† Trans. Amer. Ophth. Soc. 1869, pp. 71—75.

‡ Retinitis hemorrhagica bei Diabetes Mellitus. Zehend., Klin. Monats., 1873, xi, s. 291—298. An abstract of this and other cases will be found in "Periscope," parts II and III of preceding volume.

hæmorrhages into the vitreous. These occur equally in the cases where the diabetes is, and where it is not, complicated by albuminuria. Hæmorrhages into the vitreous are of rare occurrence in pure cases of albuminuric retinitis, so far as I know. They appear to be frequent in glycosuric retinitis, and are recurrent.

As to the cause of the changes in the retina and vitreous, there remains a certain degree of obscurity. Prof. Leber, in discussing these, considers that they may be due in part to the diabetes, in part to nephritis caused by the latter, or to the two combined. But, as he says, how diabetes brings about the changes is quite unexplained, as moreover, is the cause of the retinal affection in Bright's disease itself. But we find in by far the majority of instances of retinal disease that they are associated with lesions of other organs or with altered blood conditions and disturbances of nutrition. From the analogy of Bright's disease, in cases where the lesion is not due to renal affection, one is led to look to other organs in search of an explanation. The brain and the heart suggest themselves as possibly at fault. As regards the brain, the retinal changes met with in diabetes differ from the neuritis or neuro-retinitis usually associated with cerebral disease. Cases are met with, it is true, where changes almost precisely like those encountered in albuminuria are associated with coarse lesions of the brain, such as tumour, &c., but these are rare. Still, there may be some connection between the diabetes and the retinitis. Either the brain lesion may be primary, and cause both the diabetes and the retinal affection; or, on the other hand, the diabetes may be primary and cause both the retinal and the cerebral affections. These different classes of cases Prof. Leber has, he thinks, been able to distinguish in connection with the affections of the optic nerve in diabetes. Encephalic lesions, thus, do not appear to explain all the cases, and we turn to the heart in search of a cause. In the published cases, though the details in the records on

this point are few, there is nothing to support the idea that the hæmorrhages are connected with any heart affection, as in some forms of hæmorrhagic retinitis. In my case, about to be related, there was no hypertrophy or other sign of cardiac disease. Failing to find any adequate cause for the retinal changes in any of the viscera, we are driven, as Prof. Leber says, to compare diabetes with other morbid conditions attended by a like alteration in the retina, such as Bright's disease, pernicious anæmia, hæmophilia, purpura, leuchæmia, &c. In all of these diseases there is an undoubted alteration in the blood, and, in some at least, changes in the vessels, in consequence of which diapedesis of coloured corpuscles and transudation of abnormally constituted albuminous matters take place. Such alterations are not limited to the retina, but are generally found also in the brain, spinal cord, and many other parts of the body. Their wide distribution is evidence in favour of a common origin in a blood dyscrasia. Dr. Dickinson has discussed very ably* the relation between the changes he finds in the nervous centres, and which resemble the appearances seen in the retina and the glycosuria. I cannot help differing from his conclusions, however, for Dr. Dickinson regards the perivascular extravasations and erosions of nervous structures as the cause of the symptoms in diabetes. To my mind the whole evidence points to the changes in the nervous system as well as those in the retina and other organs, being due to an altered condition of the blood. If the retinal changes found in diabetes are not due to an antecedent brain lesion, but are dependent on the same cause as the latter, then the fact that glycosuric retinitis only occurs when diabetes has been some time in existence, becomes valuable as enabling us to correctly interpret the changes found in the nervous centres. From what we know of the other diseases where similar changes are found in the retina and

* Diseases of the Kidney. By W. Howship Dickinson, M.D. 1875.

in the nervous centres, such as pernicious anæmia,* hæmophilia,† purpura,‡ leuchæmia,§ ague,‖ the alterations in the nervous centres and in the eyes would appear to be coincident, rather than the latter sequential to the former. I think, therefore, we may justly infer, that the perivascular hæmorrhages, extrusions, excavations, and atrophies are the consequences and not the causes of the altered condition of the blood—I do not say the glychæmia—and blood vessels incidental to diabetes.

The following is the case to which I wish to direct attention :—

A woman (A. R.), æt. 52, admitted under my care into the London Hospital, December 15, 1875. Married; had neither children nor miscarriages. With the exception of an abscess of her knee-joint at 18 years, had no important illness; but had been subject to frequent attacks of diarrhœa, and suffered from rheumatic pains. The menopause occurred three years before admission. Her mother died of "galloping consumption;" her father through a severe cold. She had a brother living, but delicate.

She gave a rather confused and contradictory account of her illness, most of the facts having to be elicited by direct questions. In this way it was gathered that about three months before coming to the hospital, she went one day to look at the clock, and found she could not see what time it was with the left eye, and only with great difficulty with the right. This was the first time she experienced any defect of sight. Not being able to see the clock properly, she took a book in her hand and tried to read. She quite failed to do so with the left, and could not read at all plainly with the right eye. Shortly after this, as her sight

* Immerman, Deutsche Arch. f. klin. Med., 1874, xiii, 209-244. Manz. Veänderungen in der Retina bei anæmia progres. Centralblatt. f. d. med. Wissensch., 1875, No. 40, s. 675.

† Wickham Legg. Report from Post Mortem Room, St. Barth. Hosp. Rep., 1875, p. 64. Author. Med. Times and Gaz., March 10, 1877.

‡ Rec. Union Med., 1870, No. 48. Author. Med. Times and Gaz., March 3rd, 1877.

§ Poncet. Arch. de Physiol. norm. et Path., 1874, p. 496, and most ophth. writers.

‖ Author. Retinal Hæmorrhages and Melanæmia as Symptoms of Ague. Med. Times and Gaz., June 23, 1877.

did not improve, she came to the Ophthalmic Department of the London Hospital, and was seen by Mr. Waren Tay. Mr. Tay found hæmorrhages into each vitreous, obscuring the view of the fundus. In the left this was so much the case that nothing could be seen but an indistinct large white patch in the situation of the disc, with angular processes passing from it. In the right the margin of the disc could be made out, and did not show evidences of neuritis. Near the disc, below and to its outer side (inverted image) was a patch of extravasation of considerable size. Other smaller hæmorrhages could also be seen, but no white spots or patches. On examining the urine (when brought subsequently) Mr. Tay found marked evidence of the presence of sugar. The woman's health was failing, and her sight became so bad that she could not find her way about. Treatment of the diabetes afforded her only chance of improvement, and she was transferred to my care as an in-patient. At this time she could not read the largest test-type, and could not easily count fingers held in front of the eyes, but could distinguish the checks on the coverlet of her bed.

On inquiry it was elicited that about 12 months before admission she experienced severe pain in her back, especially in the region of the right kidney, accompanied by great thirst. Shortly after this she noticed that she passed a large quantity of urine, more than a couple of quarts a day. Her appetite was good, but not ravenous. In this state she continued up to admission, gradually losing flesh and strength, especially towards the latter part of this period.

On admission I noted that the patient was of short stature (4 feet 9½ inches), fairly nourished, yet somewhat wasted; weight 6 stone 10½ lbs. Her hair was plentiful, of a dark brown, turning grey, eyes greyish brown, complexion florid, lips of good colour; tongue small and pointed, coated with silvery fur on dorsum, but red at tip and edges; teeth few, those remaining in good state of preservation. There were no abnormal physical signs in chest, except a hyper-resonant percussion note and prolonged expiration, denoting vesicular emphysema. Owing to the latter, the cardiac dulness was masked. The heart sounds were natural. Pulse small, but rather resistent, the sphygmograph indicating a slight increase of arterial tension. Hepatic dulness in the right mammary line commenced at lower margin of sixth rib.

and did not extend beyond the margin of the costal arch. Splenic dulness not increased. Abdomen soft and flaccid. There was slight œdema of the feet. Her temperature was almost invariably below the normal, being generally between 97° and 98°. She passed on an average 3,000 cub. cent. of urine daily (rather over 100 ozs.), the maximum quantity being 4,000 c.c. The urine was pale and clear, and always had an acid reaction. Its specific gravity varied between 1,034 and 1,040. It contained on an average from 10 to 12 per cent. of sugar, giving about 380 grammes as the total quantity of sugar excreted per diem. The quantity of sugar varied somewhat, and rose (to about, on an average, 400 grammes) when she had been in the hospital a short time, with a liberal dietary. The largest quantity of sugar passed in one day was 666 grammes. She passed about 34 grammes of urea per diem, a quantity considerably in excess of the proper amount for a person of her weight. Her urine always contained *a trace of albumen*—never more than a trace. I have no mention of the presence of casts, which may be accepted as evidence that there were none, for the urine, I believe, was examined on several occasions microscopically. When the patient came under my observation the lenses were quite transparent, but the fundus was so obscured by the vitreous hæmorrhages that but few details could be seen. Mr. Couper saw the patient about this period, and his description accords with that of Mr. Tay, and with what I with less certainty made out. Mr. Couper reported: "In the *right eye* there are two large floating films in the vitreous; from their reddish-brown tint they are obviously altered blood clot. The vitreous itself is fairly translucent, yet turbid enough to conceal nearly all details of the fundus. There can, however, be seen an opaque, whitish, linear projection into the vitreous, on which retinal vessels are visible, and to which one of the filmy floating webs is attached. *Left eye:* the vitreous has all the appearance of having had diffuse hæmorrhage into it. It absorbs light strongly. The only visible detail of fundus is a glistening white crescentic mark, on which no vessels are visible, and which appears to be near the disc, but which cannot be identified with it. No visible floating material in vitreous. Tension fairly normal."

After being left on a mixed dietary for a week, her urine was tested hourly one day, for 14 consecutive hours, to ascertain the

period after ingestion at which the maximum amounts of sugar, urea, and water were excreted. It was found that the largest quantities of urine and sugar were passed at the third and fifth hours after a mixed meal, she having fasted 14 hours previously to this. At the third hour the quantity of urine was 250 c.c., and the sugar 31 grammes; at the fourth hour the urine fell to 80 c.c., and the sugar to 9 grammes; and at the fifth hour the urine rose to 200 c.c., and the sugar to 25 grammes. The urea did not follow so exactly the rise and fall of the urine and sugar, as it frequently does in diabetes; she passed about a gramme of urea an hour. At the eleventh hour after food there was a marked rise in the amount of urine, of sugar, and of urea, the latter reaching its maximum for the day—2·1 grammes in the hour.

On January 6th all starchy and saccharine substances were removed from her dietary, and she was ordered gluten bread, green vegetables, two eggs, four pints of milk, and three ounces of whisky per diem. A week later she said she felt better—not so sinking as she had previously felt; her thirst was less; she did not perspire; she had an acid taste in her mouth.

On January 31st, 1876, whilst still on an almost purely nitrogenous diet, she was ordered a grain and a half of carbolic acid, in a pill, three times a day; and on February 14th the dose was increased to two grains. During this period her general condition improved; her thirst was less; and she passed, if anything, rather less urine and sugar; the quantity of the latter daily excreted was about 250–260 grammes. Her weight increased from 6 stone 10½ lbs. to 7 stone 7½ lbs., which latter was reached at the end of February. From this time her weight decreased, and it will be seen that untoward symptoms made their appearance coincidently with this. There was no material change in the various constituents of the urine, which contained much sugar and a trace of albumen to the end.

Her appetite was never excessive; she never had diaphoresis. On February 17th she complained of shooting pains in her legs. On March 13th it was noted she had not been so well the last two days. Her face was flushed, though her temperature was slightly below normal. She slept badly; had fallen off in her appetite. She complained of "rheumatics" in her knees and ankles. On March 15th she felt weak and giddy, and could not stand. She vomited once; cared for no food. The carbolic acid was discon-

tinued, and a stomachic ordered. On March 22nd she drew the attention of Mr. Williamson, the house physician, to a twitching of the right leg, which she said had been going on for nearly a week. At my visit, the next day, she was lying in bed, with a very flushed face. The latter had a bright red congestive look, like a very rosy apple, and the redness was most marked over the natural prominences of the face, such as the nose, cheeks, and chin. Her tongue was coated with a whitish fur, and she complained of thirst. Her urine was noticed on this day to have a smoky tint, suggestive rather of carbolic acid poisoning than of hæmaturia. She had not taken any carbolic acid since the 15th, however, and this was the first occasion that the urine had presented this appearance. It had not a peculiar smell. There was a convulsive twitching of the muscles of the right leg and foot, by which the latter was extended and adducted by a succession of discontinuous spasms. She had pain in this leg and tenderness on pressure over the tibia. There was slight twitching of the left leg, but no pain or tenderness. There was slight pitting on pressure over both feet. Mr. Tay examined the eyes ophthalmoscopically on this day. He noted there was a "red reflex from all parts of the right fundus, except an undefined white patch in the region of the disc. The left fundus gives no reflex whatever—looks quite dark. Pupils (as usual, I may add) only moderately dilated." Up to the time of her taking to her bed, she had been able to make her way about the ward, more by the exercise of her senses of feeling and hearing than by sight. It is curious to contrast Mr. Tay's observation with the following statement of the patient on this day. She said she always felt as if there was a black hat over both eyes when she looks upwards, not when she looks forwards. When the left eye is closed she still sees the black hat, but when the right eye is closed the hat disappears, and she sees fairly well. She was ordered a mixture containing 15 grains of bromide of potassium and half a drachm of aromatic spirits of ammonia, in water, three times a day. Her condition remained stationary for the next few days; she had the flushed face and twitching of right leg.

On the 29th of March, Mr. Williamson was called to the patient at 6.30 a.m. The sister said that at 5 a.m. the patient became almost insensible very suddenly. A little whisky was given, but she continued to get worse, and when Mr. Williamson

saw her she was lying on her back, quite unconscious, with her eyes closed. When the eyelids were separated, the eyes were seen to be divergent; the corneæ were insensitive; the pupils were under the influence of atropine. Her breath had the odour of whisky. The pulse could not be felt at first, but a few minutes later it was just perceptible: it was then 120, regular, and extremely small. The respirations were 40 in the minute, and regular. They were deep and sighing; the chest rose with each inspiration, the mouth opening, and the head moving back. The redness of the cheeks, nose, and chin was less than during the past few days. The whole face had a dusky hue. The movement in the right leg had ceased. The surface of the body was moderately warm. She remained much in the same state until death, which took place at 7.30 p.m.

Autopsy: Body not much wasted. There was found a quite recent hæmorrhage, about the size of a wood nut, in the right *thalamus opticus*. No other noticeable changes in the central nervous system. The *lungs* were congested; they weighed 2 lbs. 3 ozs., and were free from pneumonic and phthisical changes. The *heart* weighed $7\frac{3}{4}$ ozs.; the left ventricle was moderately contracted; the valves and orifices were healthy. The *kidneys* were larger than natural, and weighed $13\frac{1}{2}$ ozs. The enlargement seemed to be due in great measure to increased thickness of the cortex, suggestive of some tubular disease. The *liver* weighed 3 lbs. 5 ozs.; the *spleen*, 4 ozs.; neither presented microscopic signs of disease.

Microscopical Examination.—In the *convolutions of the brain*, the principal changes are dilatations of the perivascular spaces. The spaces have irregular borders; in no case are they very large, not larger than three or four times the diameter of the contained vessel. Within the spaces, at parts, yellowish-brown granules are often encountered, generally in contact with the walls of the vessels. This pigment, from its colour, arrangement, and position, would appear to be altered colouring matter of the blood. Nowhere are seen unaltered coloured blood corpuscles outside the vessels, nor are blood crystals met with. Some of the larger veins are distended with coloured and colourless blood corpuscles, and surrounding many of the vessels are numerous small round cells, with one or two nuclei, which stain deeply with hæmatoxylin—colourless blood corpuscles—which have wandered from the

vessels. The arteries are for the most part healthy; the muscular coat is not thickened, nor are the nuclei proliferating. Only in a few places are noticed the hyaline changes of the intima, to be described more fully in connection with the vessels of kidney and spleen. The capillaries present no alterations. The perigangliouic spaces are almost uniformly dilated.

Medulla Oblongata: Here the changes are very like those described in the convolutions, only the hyaline change in the arteries is more pronounced. The hyaline degeneration is mainly confined to the elastic portion of the intima. The endothelium presents no changes, but is sometimes separated from internal elastic coat. The hyaline change does not as a rule invade the middle coat of the vessels. The perigangliouic spaces are much dilated; the ganglion cells being sometimes shrunk, sometimes retaining their normal size. The ganglion cells, especially when shrunk, are in parts deeply pigmented, of an almost mahogany-brown colour, and their outline is indistinct.

Pons Varolii: Same changes as in medulla; the perivascular infiltration with lymphoid cells is greater, however. Veins are met with filled with colourless corpuscles; but from there being no bulging of the walls or signs of stasis, this would not appear to be due to thrombosis. Some of the capillaries are markedly dilated, but for the most part uniformly so; only in a few places can any unequal dilatation of these vessels be seen, such as would deserve the title of capillary aneurism.

Kidney: Several important changes are met with here, but I will describe these with as great brevity as possible. First, as regards the uriniferous tubes. A noticeable feature is a dilated condition of the tubes almost throughout the whole of their varying course. This is well seen, for the membrana propria stands out conspicuously, the cells often being detached from it. In some parts the membrana propria is thickened by hyaline change. For the most part the secreting epithelium is well preserved, but in parts it is granular and indistinct. In the large collecting tubes of papillary portion, the epithelium presents very peculiar changes. In some of these tubes it has a beautiful, perfectly translucent appearance. The cells are swollen, and their outline is as distinctly marked out as in a nitrate of silver preparation. The cells are so translucent that there appears nothing to hold the nuclei in position. The nuclei, in some of these

altered epithelial cells, are of natural size, and well stained by hæmatoxylin; in other cells they are swollen to three or four times their natural size, and are pale and vesicular. They present all transitions between these two states, and the advanced stage reminds one of the swollen vesicular condition of coloured blood corpuscles when treated with water. The epithelial cells suggest the idea of having had all but the skeletons of the cells washed away, and there can, I think, be little doubt that the appearances I have described in the epithelium of the collecting tubes are due to the constant irrigation to which they were exposed. In other collecting tubes the epithelium is detached, and the lumen contains granular matter. Probably this is a later condition of the former change. Some of the tubules contain hyaline or fibrinous casts. There is a small amount of lymphoid infiltration at the bases of the pyramids. In the arteries a very conspicuous change is met with. It is most pronounced in the smaller arteries—the glomerular (afferent) arteries. These vessels are enlarged in an irregular way, and their walls greatly thickened. The increased thickness of the walls is mainly limited to the intima of the vessels, and consists of a hyaline transformation of this coat. The endothelium is, for the most part, intact, not swollen or altered in appearance. Sometimes it is crumpled up into a fold in the lumen of the vessel, and sometimes, whilst the individual cells preserve their mutual cohesion, it is detached from the rest of the intima. Between the endothelium and the muscle layer is a hyaline, yellowish-brown material, closely resembling in appearance the hyaline or fibrinous casts in the tubes, whilst their change involves the whole of this portion of the intima. Whilst this change involves the whole of this portion of the intima, it is rarely evenly distributed, but forms excentric bulgings at different points. The bulging is almost always towards the lumen of the vessel, which is in consequence greatly narrowed, or even obliterated. On transverse section of these vessels the lumen is often represented by an irregular space with crenated margin, the nuclei being brought very close to each other. When excessive, however, it bulges also outwards, so as, in a longitudinal section, to form a fusiform or biconvex enlargement of the wall of the vessel. Though usually confined to the intima, in some cases it involves the muscular coat, the purple stained nuclei of which may be recognised in its midst. The change usually commences just

where the afferent arteries are given off from the trunk of the interlobular arteries, the walls of the latter up to the very point where the altered afferent arteries leave them being generally unaffected. Sometimes, however, the interlobular arteries are markedly affected by the hyaline change, and here the bulging has as great a tendency outwards as towards the lumen of the vessel, appearing on longitudinal section as a plano-convex swelling. Here, too, the swelling is partial, different portions of the same vessels being affected in unvarying degrees. The hyaline change accompanies the glomerular (afferent) arteries throughout the whole of their course, generally ceasing at the point within the Malphigian corpuscles, where the vessel breaks up into capillaries. In the majority of cases the glomeruli are scarcely, if at all, affected; sometimes slight changes, similar to those in the arteries, are seen in the capillary network, rendering this indistinct. In some few instances the glomeruli have undergone atrophy, being reduced to a more or less fibrous body, in which are scattered a few nuclei. The latter change is similar to what is seen in a late state of interstitial nephritis. Sometimes, however, there is a slight increase of the glomerular nuclei. The muscularis is not thickened, unless it shares in the hyaline transformation. There is no increase in the thickness of the adventitia. The veins present no noteworthy changes. The capillaries are usually widely dilated, though for the most part empty. There are numerous deposits of amorphous matter staining purple with hæmatoxylin scattered about the kidneys, probably lime salts.

Spleen: The most conspicuous change in this organ is the hyaline degeneration of the arteries. This is extremely general, and very pronounced. It is confined to the arteries, especially the smaller ones. Many of these are completely obliterated along a considerable portion of their track by the walls being brought into apposition. Though the walls meet, they nowhere cohere. As in the kidney, the change is generally confined to the intima, though, in some instances, it also involves the muscularis. The endothelium is unaffected by the change, through sometimes stripped from the swollen elastic membrane. The swelling is irregular and excentric, in transverse section often appearing nodular. The hyaline material is almost of the same colour as that met with in the kidney; if anything, more yellow and refractive. Here, however, it has a tendency to separate by

cleavage into fibrillæ or lamellæ. I cannot decide whether this cleavage is determined by the position of nuclei. The adenoid sheaths of the arteries and the Malpighian corpuscles are somewhat enlarged, and present slight hyaline degeneration at the part immediately surrounding the altered arteries. *Liver:* There is atrophy of the liver cells which are found in various stages of fatty, granular, and pigmentary degeneration. The vascular and lymphatic capillaries are generally dilated. Some of the smaller branches of the hepatic artery show slight hyaline transformation of their intima. *Pancreas:* Epithelium more granular and indistinct than natural. Some deposits of amorphous and crystalline matter, taking a purple stain with hæmatoxylin—lime salts probably. Hyaline changes in the intima of some small arteries. *Heart:* Muscles fairly good; no important changes.

The posterior halves of the *eyes* were carefully removed. Large hæmorrhages in the vitreous were seen with the naked eye and the retinæ appeared thickened. After examination the globes were placed in preserving fluid and handed to Mr. Nettleship, who reports as follows:—

Microscopical Examination of the Eyes by Mr. Nettleship.

The principal changes discovered may be conveniently grouped into those in (*a*) the retinal and choroidal membranes and the vitreous; (*b*) the subvaginal lymph-space of the optic nerve and in the nerve itself; (*c*) and lastly, in the arteries and capillaries of the nerve, retina, and other parts.

(*a*) The *retina* was thickened in all its layers, the change being greatest in the nerve-fibre layer where there were numerous varicose swellings; the disc slightly swollen and its nerve-fibres converted into an intricate meshwork of fine threads, the meshes being for the most part empty, but sometimes filled by swellings like those in the retina. The thickening of the other retinal layers appears to be the result of chronic œdema with hypertrophy of the connective framework. The ganglion cells and the granule layers are well preserved, and indeed more readily seen than usual, their elements having been, as it were, dissected apart by the effusion of fluid between them; the fibres proceeding from the ganglion cells beautifully seen. Bacillar layer wanting and its place in some parts occupied by a layer of albuminous effusion. In the intergranule and molecular layers are here and there

round spaces (microscopic cysts) filled with large faintly-refracting globules (albuminous). *Limitans interna* much thickened in parts, and thrown into abrupt folds, which, when deep, resemble papillæ. The retina was much more thickened in the left than in the right; in the former it measured from two to three times its normal thickness. There were no distinct hæmorrhages in the retina, only one or two small patches of rusty-looking granules being seen near the disc.

The *vitreous* in the left eye contained a large quantity of blood, apparently of different dates, and forming a dense layer lying upon the *limitans interna* of the retina. The more superficial (vitreous) part often shows distinct lamination, the lines of which are sometimes arranged so as to suggest that the bleeding took place from different spots in a gradual manner, one mass of blood thus being intruded into another. The deepest (retinal) part of the clot contains many large dark rust-coloured nucleated corpuscles (resembling the cells of the vitreous) and granules (degenerated blood). Some of these coloured corpuscles and granules lie between the layers into which the thickened *limitans interna* is often split up. The source of the blood could not be traced.

The *choroid* at the margin of the optic disc is unaltered, but immediately on leaving that line it begins to thicken. The thickening increases rather rapidly, until at a distance of about one and a half or two discs' breadths from the border it is five or six times greater than normal; after this point it remains about the same. The change is greatest in the deep vascular layer, least in the chorio-capillaris, and intermediate in degree in the supra-choroidal space. It is caused (1) by great distension of the large vessels, both arteries and veins; and (2) by the collection of faintly-granular albuminous substance in the stroma between the vessels and in the elongated spaces of the *membrane supra-choroidea*. There is slight and doubtful increase of the colourless lymphoid corpuscles of the choroid.

(*b*) The trabecular tissue of the *subvaginal lymph-space* of the optic nerve is much increased in bulk, partly by thickening of the individual cords, partly by increase in their number. Excepting at the extreme ocular end of this space, there did not appear to be any increase of the cells clothing the trabeculæ, and even there this change was not great. The inner sheath of the nerve was somewhat thickened.

The *optic nerve* showed no very marked alterations. Its connective-tissue nuclei were increased in number in and just behind (= on the brain-side of) the *lamina cribrosa;* and further back (as far as three-fourths of an inch from the eye) they were unusually conspicuous, apparently from being somewhat swollen. The nerve-fibres were unusually varicose, and as the eyes were removed shortly after death in cold weather, it is probable that this was not altogether a *post-mortem* change.

(*c*) The most interesting changes are those in the blood-vessels, and although these are essentially similar to the changes in the vessels of the other organs examined by Dr. Mackenzie, a description of them will be of interest from the ophthalmological point of view. I must add that I did not fully observe and appreciate the vascular disease in the eyes until Dr. Mackenzie had shown and explained to me his preparations from the spleen, kidney, and other parts.

It is to be noted first, that there was great distension of all the vessels in the choroid and retina, as well as of the branches of the ciliary arteries surrounding the optic nerve in the sclerotic and of the nutrient arteries of the optic nerve-sheath.

The special changes in the arterial coats were, however, much more marked in the *arteria centralis* and its branches than in the scleral vessels, and were scarcely present at all in those of the choroid. The best marked alteration consists in a thickening of the layer immediately external to the endothelium, and this may occur either uniformly for a long distance or in circumscribed portions. Thus in the trunk of the *arteria centralis* there is a long tract of thickening between the endothelium and the fenestrated membrane, affecting, however, only one side of the vessel (as seen in longitudinal section) and rather suddenly increasing at one part so as to form a considerable swelling by which the lumen is notably contracted (Fig. 1); (a second and quite similar swelling is present lower down in the same vessel). In the retinal branches of this artery the thickening is much more general, although varying greatly in degree in different branches. As a rule the relative thickening of the coats is much greater in the very minute arteries than in those of larger size (Figs. 2, 3, and 4). In an early period the new material is more or less distinctly corpuscular (Figs. 1 and 2), and its innermost portion sometimes appears composed of superimposed layers of endothelia

(Fig. 1). In many specimens, where the disease is apparently of older date, the appearance is best described as partly hyaline and partly fibrous (Figs. 3 and 4), the hyaline change being most

Fig. 1.

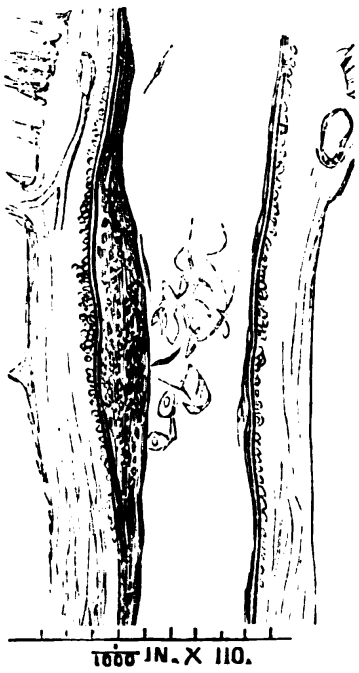

Fig. 2.

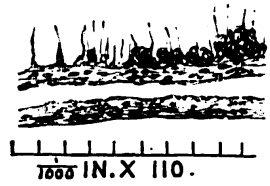

Fig. 3.

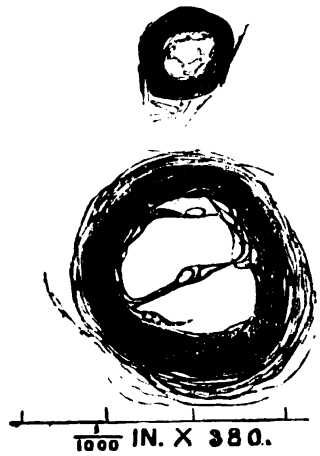

Fig. 4.

Fig. 1. *Art. Centr. Retinæ.* Longitudinal section. Upper end of drawing is at level of deepest part of *lam. crib.* Thickening of one side of vessel, and narrowing of lumen from nucleated growth between endothelium and elastic lamina; detachment of endothelium; (?) increase of muscle cells opposite thickest part of swelling.

Fig. 2. A rather small artery from nerve fibre layer of retina. Müller's fibres and ganglion-cells bound one margin (the upper in the figure). Thickening of the entire arterial wall, with separation and some obscuration of nuclei (this point not well shown in the woodcut).

Figs. 3 *and* 4. A minute and a medium-sized retinal artery seen in transverse section. Hyaline thickening of coats with indistinctness of the muscle nuclei; in the large vessel a more fibrous appearance. Alteration of the endothelium.

obvious in the smallest vessels. The endothelium is often separated in single cells or in irregular sheets (Figs. 1 and 4), and in the smallest vessels sometimes looks as if swollen (Fig. 3). The

relation of the muscular coat to the morbid change is not easy to make out in all cases. In such a vessel as is depicted in Fig. 2 it appears that the whole vascular wall external to the endothelium is swollen, but on examination with high power no evidence of increase in the muscle-cells is apparent; rather the whole tissue appears swollen and dim, the nuclei being less apparent than in health (the nuclei as represented in the woodcut are too conspicuous). In others (as seen in Fig. 1) there is some increase of corpuscular elements in the situation of the muscular layer just at the part where the greatest internal thickening is present. In the more hyaline vessels (Figs. 3 and 4) it is difficult to make out any trace of the muscle layer, only a few obscure nuclei being visible. A uniform thickening of the fenestrated membrane is the only change visible in a tolerable number of arteries.

The veins as a rule are merely distended, their coats not altered. Some of the large branches on the disc, however, pre-

Fig. 5.

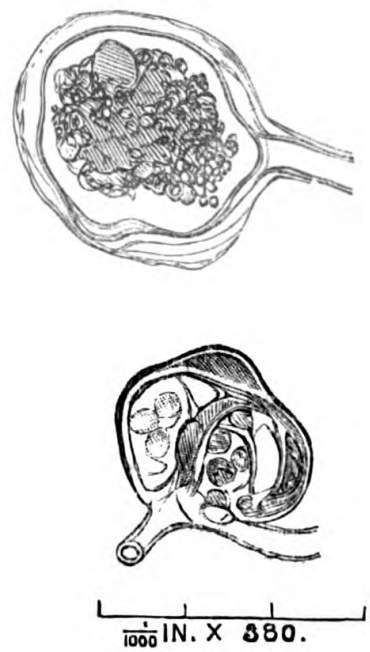

Fig. 6.

Figs. 5 *and* 6. Two retinal capillary aneurisms. One contains a mass of brownish-red granules of various sizes. The other is (or appears to be) chambered by septa or bands, probably altered endothelia; some globules of albuminous matter and altered blood corpuscles seen in its cavities.

sent numerous cells like leucocytes, in and immediately outside their coats; this, which is a perfectly definite change when it occurs, is noticed in only a few of the veins. It may here be noted that some of the blood-vessels in the tissue outside the sclerotic were surrounded by circular thin-walled spaces, probably distended lymphatic sheaths.

The capillaries of all parts are distended. In the retina there are minute aneurisms on the capillaries. These are not very abundant; they often occur in little groups of about half a dozen or less near together, large adjoining tracts being quite free from them. They are globular pouches, apparently communicating with only one side of the vessel; never fusiform dilatations (Figs. 5 and 6). They usually contain some reddish-brown granules, and sometimes similar granules are seen lying in the tissue just external to them, suggesting that the bleeding into the vitreous may have been due to the consecutive rupture of a number of these minute sacs. One of them appears to be divided into chambers (Fig. 6). The capillary walls are as a rule not much, if at all, thickened, but here and there considerable thickening is seen.

It will be seen that the eye-disease first manifested itself in a characteristic manner by disturbance of vision; and that polydipsia and polyuria had preceded the ocular symptoms for about a year. The diabetes was severe, as evidenced by the amount of urine and sugar daily excreted. The patient generally passed about a pound of sugar per diem, and sometimes considerably more. Further, the patient died, whilst her blood was loaded with sugar, with that peculiar form of coma which has been termed "diabetic coma," or "coma-collapse," and which has been attributed by Kussmaul* and Rupstein† to the development of acetone in the blood—*acetonæmia.*

It may be thought that death was determined by cerebral hæmorrhage, for there was an extravasation into the

* Zur Lehre vom Diabetes Mellitus, Deutsch. Arch. f. klin. Med., 1874, xiv, 1–47.

† Centralblatt f. die Med. Wissensch., 1874, No. 55, s. 865.

right thalamus; but I do not think this had necessarily or exclusively to do with the coma. I have watched several other patients die in quite a similar manner, and on *post-mortem* examination, no gross change, such as hæmorrhage, has been found. This is also the general experience. The hæmorrhage found was recent, and was on the same side as the convulsive movements noticed in the right foot. It could not, therefore, have given rise to the latter, though the cause of these movements was not discovered. The cord has not been carefully examined microscopically. It will be observed that the patient's urine contained albumen, and it becomes of importance to try and determine what share, if any, the kidney had in producing the retinal changes and extravasations into the vitreous. It will be noticed that the urine contained only "a trace" of albumen throughout the observed progress of the case. It was daily examined. There was, also, slight œdema of the feet. The kidneys were larger than natural on *post-mortem* examination, and the increase was mainly of the cortex. The microscope shows slight changes in the tubes, and a very slight degree of intertubular infiltration. These changes undoubtedly indicate a very slight amount of parenchymatous and interstitial nephritis, and are quite in harmony with the persistent presence of a small quantity of albumen in the urine, and the œdema of the feet. But the renal affection was really very slight, and the kidneys were able to perform their functions, as evidenced by the amount of urea daily excreted by them. A further proof that the kidney disease was not severe or of long standing, or that the general vascular degeneration—"arterio-capillary fibrosis"—was non-existent, is that no hypertrophy of the heart was present. The amount of renal disease appears no more than their overtaxed functions would be likely to induce. The increased bulk of the kidneys (the two weighing 13½ ounces), was mainly due to the dilated condition of the uriniferous tubes and blood-vessels. There was a peculiar change in

the arteries of the kidney, but this is distinct from the changes usually met with in Bright's disease. There, therefore, appears no clear evidence that there was such an amount of renal disease as to call forth secondary changes, like retinitis. For the same reason, there is nothing to warrant the opinion that the coma was due to uræmia. I think, therefore, we are justified in excluding the kidneys as the cause of the changes in the retina and vitreous. There was no disease of the heart to account for the hæmorrhages. As regards the minute changes in the intra-cranial organs, they are slight and similar to what have been noticed before,* with the exception of the hyaline change in the intima of the arteries. Similar vascular changes are also found by Mr. Nettleship in the retina, but are not peculiar to, or most marked in, nervous structures. With reference to this hyaline change of the intima of arteries, from my description it will be seen that, though widely distributed, it is most marked in the kidney and spleen, and its nature can be best studied in those organs. It seems to be a peculiar transformation of the elastic portion of the intima, though it sometimes, as Mr. Nettleship has noticed in the retina and optic nerve, and I have observed in the kidney and spleen, extends beyond these limits and invades the muscular coat. The material in question has a peculiar faint yellow to yellowish-brown colour in logwood preparations, is somewhat highly refracting, and appears homogeneous, with a tendency to become fibrillar. It is not acted on by iodine or methylaniline in a similar manner to amyloid or lardaceous material. This change is a very interesting and important one. It is identical with what Dr. E. Klein has described in the arteries of the kidney and spleen in scarlatina,† and in the spleen in enteric fever.‡ Fr. Neelson§

* Dickinson, loc. cit.

† Reports of the Medical Officer of the Privy Council. New Series, No. VIII.

‡ *Ibid.*, No. VI.

§ Archiv der Heilkunde, 1876. Heft ii und iii, s. 119.

has noticed a somewhat similar change in the capillaries of the pia mater in some of the acute infectious diseases and in various other diseases (syphilis, phthisis, pneumonia, dysentery, rheumatism, &c.); and other observers have noticed colloid or glassy degeneration of arteries and capillaries of the pia mater in connection with brain diseases. The change in my case exactly corresponds with what Dr. Klein has so well described and delineated, in connection with scarlatina and enteric fever, with what I have found (in the spleen) in all the cases of pyæmia I have examined, and with the appearances seen in a case of sub-maxillary cellulitis (angina Ludovici) I have investigated. I can quite corroborate Dr. Klein's statement that the change is external to, and independent of, the endothelial lining of the arteries, and that it is situated in the elastic membrane of the intima. The change, Neelson observed, is similar to the "hyaline fibroid" change of the adventitia, first described by Sir Wm. Gull and Dr. Sutton,* from which this change in the intima is distinct. I have found this change in a slighter degree in other cases of diabetes, but am not aware of its having attracted other observers' attention.

Though this hyaline transformation of the intima well deserves, from its effects, the title of "obliterative arteritis," it is quite different from the "obliterative arteritis" described by Friedländer,† or the change identical to the latter, described by Heubner,‡ under the name of "syphilitic degeneration of the cerebral arteries." The change in the intima of the renal arteries, in my case, is greater than in any case of scarlet fever I have seen, or in cases of pyæmia. It is interesting to note that in most of the diseases it is met with, there is some profound alteration in the blood; and this altered condition of the blood, and of relation between blood and blood-vessels, may

* Medico. Chirurg. Trans. 1872, p. 273.

† Centralblatt f. d. med. Wissensch. 1876, No. 4, s. 65.

‡ "Ueber luetische Erkrankung der Gehirnarterien," Leipzig, 1875.

have something to do, also, with the hæmorrhages. It is noteworthy that Dr. Klein has met with the hyaline change of the arteries and capillaries most marked in early cases of fatal scarlatina, before there is any interstitial nephritis, and he finds no reason to believe there is any relation between the two. In most of his cases there was no albumen in the urine. He also finds in scarlet fever proliferation of the muscle nuclei in vessels presenting this change, though not limited to these. In my case, there is no increase in the muscle nuclei.

The occurrence of similar hyaline changes in the arteries of the retina (as illustrated in the woodcuts) is a point of much interest; although it must be remembered, that the changes are not so pronounced in the retina and optic nerve as in the kidney and spleen, more resembling those in the liver and pancreas. But a point of still greater importance is the existence of aneurisms of the retinal capillaries. Their existence may serve to explain, as Mr. Nettleship suggests, the hæmorrhages into the vitreous. Professor Leber is also inclined on other grounds to attribute the vitreous hæmorrhages to repeated bleedings from small retinal vessels.