THE DIABETIC EYE

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THE INTRODUCTION of insulin has transformed the management of diabetes mellitus bringing a greatly increased expectation of life with the result that a number of complications, some taking many years to develop, have become manifest. At the present time the impact of this revolution is being felt as a large population of patients with long established diabetes collects. Blindness due to diabetes has increased and diabetic retinopathy accounted for 11.3% of those under 60 years old registered blind in Great Britain in 1962 (Mooney, 1963). It seems appropriate in this article to deal at length with diabetic retinopathy and review the other ocular manifestations of diabetes briefly. For the sake of orientation the ocular changes in diabetes are listed in Table 1, while Table 2 indicates how various events may affect the eyes.

RETINOPATHY

Clinical Manifestations

Diabetic retinopathy is a disease of considerable variation both in severity, clinical appearance, and progress. It is seldom seen in the young diabetic of less than five years' duration (Collyer and Hazlett, 1961), but is often present at diagnosis in the maturity onset diabetic and may be the presenting lesion. The earliest clinical manifestations comprise a central punctate retinopathy (Ballantyne, 1947) with microaneurisms, dot hæmorrhages and small white spots grouped around the posterior pole of the eye. After a time larger hæmorrhages develop which have been likened to blots, round in shape with crenated poorly defined margins; set deeply in the retina in the inner molecular and nuclear layers, they contrast with the more superficial flame shaped hæmorrhages of hypertensive retinopathy which are moulded by the nerve fibre layer. Accompanying these hæmorrhages are small patches of waxy exudate. The retinopathy advances and spreads to involve larger areas of the retina but seldom affects the periphery of the fundus. Larger and more irregular hæmorrhages are seen which break through the layers of the retina to lie on its surface,

TABLE 1
OCULAR MANIFESTATIONS IN DIABETES

External	Lid and conjunctival infection Ophthalmoplegia
Anterior segment	Pigmentary migration Pupillary changes poor dilatation Argyll Robertson pupil Rubeosis iridis hæmorrhagic glaucoma Cataract transient changes diabetic (juvenile) senile Hypotension, in diabetic coma
Posterior segment	Vitreous hæmorrhage Retinopathy Lipæmia retinalis Optic neuritis
Subjective phenomena	Transient changes in refraction Weakness of accommodation Aura of hypoglycæmia

TABLE 2
OCULAR MANIFESTATIONS ON CERTAIN OCCASIONS

Presenting signs and symptoms	Retinopathy Cataract Transient refractive changes Ophthalmoplegia Optic neuritis
Diabetic coma	Ocular hypotension Transient lens opacities Lipæmia retinalis
Hypoglycæmia (early)	Subjective visual phenomena

preretinal hæmorrhages, or in a pocket between the retina and vitreous, subhyaloid hæmorrhages; the latter have a semi-circular outline with a fluid level above; the hæmorrhages absorb slowly over a period of weeks leaving few residual signs. Some of the larger hæmorrhages may break through into the vitreous causing opacities and reducing vision.

The extent to which venous changes occur in diabetic retinopathy varies considerably; a slight general dilatation is said to be the earliest sign of retinopathy but is difficult to detect. More definite are dilated segments, and these may be followed by the appearance of irregular beading of the veins, tortuosity and bizarre loops lying on the retina and projecting from its surface.

The term proliferative retinopathy implies the development of new vessels, a serious prognostic sign, for the majority of cases deteriorate and many become blind. Beetham (1963) found that five years elapsed on average between the onset and final stages of proliferative retinopathy. The stage at which proliferation commences varies from case to case, but there is always some venous abnormality present. New vessels grow in the plane of the retinal vessels and spread forwards into the vitreous to form delicate fronds, *rete mirabile*, commonly arising from the optic disc but also seen elsewhere taking origin from the retinal veins. Their walls are fragile so that bleeding frequently occurs into the retina and vitreous. At a later stage the fronds thicken with connective tissue to form retinitis proliferans, and in severe cases sheets of preretinal connective tissue form. Retinitis proliferans may also arise from the direct organisation of vitreous hæmorrhage (Ballantyne, 1947). Contraction of the retinitis proliferans and preretinal connective tissues leads to traction on the retina, shown by stress lines on the posterior vitreous face, and later retinal detachment.

Permanent loss of central vision in diabetic retinopathy is due to involvement of the macula by hæmorrhage, hard exudate or retinal detachment. Occasionally a frond of retinitis proliferans may spread in front of the macula obscuring vision. Complete blindness occurs from massive vitreous hæmorrhage, retinal detachment or intercurrent hæmorrhagic glaucoma.

It is difficult to summarise succinctly the natural history of diabetic retinopathy but three elements can be recognised, hæmorrhagic, venous and proliferative. Onset is usually marked by slight hæmorrhagic changes which progress and recruit hard exudates, venous changes run concurrently in varying degree, at a later stage proliferative changes may develop. An intricate clinical classification proposed by Scott (1951) expresses this variability. Larsen (1960b) makes a distinction between the retinopathy in middle-aged, older and juvenile diabetics. The middle-aged diabetic, 20-40 years old at the onset of diabetes, shows the evolu-

tion just described, passing from a punctate retinopathy to increasing hæmorrhage and confluent exudates, and in a small proportion of cases to proliferative retinopathy. The older diabetic aged over 50 years at onset has a marked tendency to develop exudative changes at the macula with the formation of confluent plaques; later, glistening crystals form and the whole plaque gradually disperses to leave a scarred area; central vision fails as the plaque develops. Juvenile diabetics with onset of disease in the first 20 years of life show several differing patterns of retinopathy. It may develop along the lines of the middle-aged diabetic, or there may be an early onset of proliferative retinopathy initiated by vitreous detachment with preretinal and subhyaloid hæmorrhages; other cases progress very slowly but develop severe arteriosclerosis over a period of 20-30 years.

Hypertension frequently complicates diabetes, and the retinopathy of hypertension may complicate the appearance of diabetic retinopathy, but there is no doubt that diabetic retinopathy is a separate entity not dependent on hypertension for its existence (Duke Elder, 1940a). Soft exudates are seen from time to time in the course of diabetic retinopathy but are less conspicuous than those of hypertensive retinopathy.

Development of a fine stippled pigmentation of the macula (Jensen and Lundbaek, 1955) is occasionally encountered in juvenile diabetics, the significance of the condition being that it is harmless and not associated with any loss of vision.

The differentiation of microaneurisms and punctate hæmorrhages can be difficult. If the lesion has a well defined spherical outline with a light reflex from the summit this is indicative of an aneurism, but such an appearance is not always seen. In other instances the duration of the lesion may help as hæmorrhages usually clear within a few weeks whilst aneurisms persist for long periods.

Fluorescein retinal photography (Dollery, Hodge and Engel, 1962) is a form of angiography in which the contrast medium, fluorescein, is injected intravenously and photographed as it passes through the retina. Studies of diabetic retinopathy (Scott, Dollery, Hill, Hodge and Fraser, 1964) reveal many more microaneurisms and new vessels than seem evident clinically (Figs. 1 and 2). Aneurisms are usually grouped and in severe cases appear like bunches of grapes clustered round a venule. After the passage of fluorescein some

FIG. 1.—Reproduction of a colour transparency of the fundus oculi showing the right superior temporal field, from a patient with diabetic retinopathy. There are numerous hæmorrhages and some small exudates. This figure should be carefully compared with Figure 2.

FIG. 2.—Early venous phase fluorescein photograph of the same area as Figure 1. The fluorescence appears white filling the whole of the arterioles but only the edges of the veins, because the blood from the periphery of the retina is not yet fluorescent. Numerous microaneurysms can be seen appearing as small white dots, many of them are invisible in Figure 1. The hæmorrhages appear as dark patches obscuring the background fluorescence.

aneurysms empty promptly, others more slowly, while others remain fluorescent for as long as ten minutes with leakage of the dye into the surrounding tissues. Similar leakage occurs from some new vessels, and to a marked extent from fronds of retinitis proliferans, whence dye passes into the vitreous. It is conjectured that this abnormal permeability may be associated with the haze in the vitreous found in active proliferative retinopathy.

Incidence

The incidence of diabetic retinopathy rises with the duration of diabetes. In a group of diabetics of all ages Larsen (1960a) found it to rise slowly during the first five years after the disease was diagnosed, then sharply; by ten years there was an equal incidence in nearly all age groups apart from patients under the age of 16 years in whom the complication was rare. Figures for the incidence of retinopathy vary widely depending in part on the criteria adopted for diagnosis; Larsen (1960a) notes an incidence reported in the literature of 30-80% after 15 years and 60-100% after 20 years.

It is difficult to ascertain how control of the diabetes is related to retinopathy. Keiding, Root and Marble (1952) found a reduced incidence in patients with good clinical control as compared to those with bad control, in groups

of differing duration of disease. A prospective survey of degenerative disease in growth onset diabetics entering the second decade of diagnosed diabetes was undertaken by Hardin, Jackson, Johnston and Kelly (1956) who calculated an index of control, taking into account both the strictness of control and the duration of treatment. When this index was plotted against the severity of retinopathy there was a close correlation for the whole group of patients with diabetes of 10-29 years' duration. Plotting merely duration of disease against severity of retinopathy produced a moderate correlation for cases of less than 15 years duration, an expression of the latent period required for the retinopathy to become manifest. However after that period the duration of disease was of little importance in determining the severity of retinopathy. Control was related to severity of retinopathy over the whole period of the investigation, in the sense that bad control was associated with severe retinopathy; the longer the duration of bad control the worse the retinopathy was likely to be. These conclusions are supported by Collyer and Hazlett (1961) who found in a survey of 100 growth onset diabetics that all cases of severe retinopathy were poorly controlled.

FIG. 3.—An injected specimen of retina showing an area of capillary closure in the centre of the photograph. A few dilated tortuous capillaries remain open; microaneurisms are seen on these vessels and those bordering the area of closure. Photograph supplied by Professor N. Ashton.

Pathology

Investigation of the pathology of diabetic retinopathy has been assisted by the development of new methods of histological examination. During the past 20 years a considerable amount of energy has been devoted to the problem. Ballantyne (1947) studying flat preparations of the whole retina rediscovered the microaneurisms. Ashton (1953) using injection techniques drew attention to the areas of capillary closure. More recently Kuwabara and Cogan (1960) using controlled tryptic digestion were able to isolate the blood vessels from the retinal tissue and study their histology in greater detail.

The use of injected preparations (Fig. 3) has revealed scattered areas of capillary closure related to the arterioles, but not localized to any one part of the retina; in these areas a few large dilated capillaries persist. Microaneurisms are found on these capillaries and also bordering the area of closure. Around the edge new loops of dilated capillaries form, derived from the venous capillaries. (Ashton, 1963).

Digest preparations allow study of the endothelial cells. In normal capillaries they are distributed regularly as a lining to the basement membrane, which splits to enclose the mural cells or pericytes scattered along the capillary. Ashton (1963) has studied the behaviour of the endothelial cells and finds that in areas of capillary closure the empty vessels are reduced to thin tubes of basement membrane, the

endothelial cells having migrated to the nearby open capillaries. Endothelial cells proliferate in response to hypoxia, a change seen in the new capillary loops bordering areas of closure and in microaneurisms.

Microaneurisms are not specific lesions of diabetic retinopathy for they are also encountered in a number of other conditions in which retinal hypoxia occurs, for example venous thrombosis, macroglobulinæmia and Eales' disease. They appear confined to the retina, for though superficially similar lesions are seen in the kidney in intercapillary glomerulosclerosis, Volk (1956) considers them to differ from retinal microaneurisms. Controversy exists about the origin of microaneurisms; most appear to come from outpouchings on the capillary wall though some at least start from dilated capillary loops (Ashton, 1951) whose contiguous walls adhere and break down. They pass through a cycle of changes (Cogan, Toussaint and Kuwabara, 1961), endothelial proliferation, deposit of PAS staining material on the basement membrane, lipoid infiltration and disintegration.

So far attention has been focussed on the vascular changes occurring in diabetic retinopathy, but Wolter (1961) and Bloodworth (1962) both stress the extent of neuronal degeneration, and Wolter claims to have demonstrated a proliferation and degeneration of antidromal nerves. Ashton (1963) has shown that areas of neuronal degeneration are closely related to areas of capillary closure.

The basic lesion in diabetic retinopathy would appear to be capillary closure. Most authorities would agree that new vessel formation is a secondary process induced by prolonged tissue anoxia; but the mechanism of capillary closure is still obscure. Earlier thoughts that this might have been due to tissue swelling resulting from a primary metabolic injury (Ashton, 1959) have not been supported (Ashton, 1963). A gradual hyaline thickening of the basement membrane of arterioles throughout the body in diabetes affects the retinal vessels and may be responsible for producing a slow ischaemia with lowered capillary pressure and closure (Ashton, 1963). Cogan and others (1961) have noted that the mural cells in the walls of the retinal capillaries are frequently degenerate in diabetic retinopathy; they postulate a specific lesion and consider that microaneurisms arise from these sites through weakening of the basement membrane. Loss of pericytes may also result in failure to control capillary tone with redistribution of the retinal

circulation and closure of some capillaries. Increased permeability of the capillaries due to endothelial injury (Ballantyne, 1945), and embarrassment of the venous outflow are other possible factors in the development of retinopathy. Finally the question remains whether the vascular changes, by no means specific, are primary or secondary to the neuronal lesions already mentioned (Toussaint, Cogan and Kuwabara, 1962).

From a discussion of the pathogenesis of diabetic retinopathy arises the further problem of the factors in the diabetic state which determine the onset of the retinopathy. An association between adrenocortical hyperfunction and diabetic retinopathy has been suggested by Becker, Maengwyn Davies, Rosen, Friedenwald and Winter (1954) based on clinical, biochemical and pathological evidence. During pregnancy hormonal changes occur which include adrenocortical hyperactivity; the onset of diabetic retinopathy and its resolution after delivery have been observed, also the worsening of established retinopathy during the last trimester followed by improvement after pregnancy. The development of retinal microaneurisms has been noted as a result of prolonged administration of intravenous ACTH to patients without diabetes. The association of deterioration of retinopathy with poor control of the diabetes can be interpreted in terms of the increase of adrenocortical activity which accompanies infection and ketosis. There is no direct test for adrenocortical hyperfunction, but the Thorn test (depression of circulating eosinophils in response to a test dose of ACTH) is negative in hypofunction. A negative test was obtained in 50% of a group of diabetics without retinopathy, but the response could be obtained with a test dose of cortisone suggesting that adrenocortical hypofunction was responsible for the failure. In contrast all patients with retinopathy gave a positive response. Indirect evidence of adrenal hyperfunction in diabetics with retinopathy, and hypofunction in those without retinopathy, comes from a determination of the free oxy-steroid excretion which is raised in cases of retinopathy and lowered in those without retinopathy. The excretion of 17-hydroxycorticosteroids is similarly altered but the changes are less marked (Maengwyn Davies, Lerman, Pogell, Stone, and Friedenwald 1956). The therapeutic response to pituitary ablation, adrenalectomy and testosterone will be discussed later; all of these measures result in a reduction of adrenocortical function.

The renal lesions of the Kimmelsteil Wilson (KW) kidney, are found in many cases of severe retinopathy; Ashton (1958) found them present in all cases examined by autopsy. Becker and others (1954) demonstrated evidence of adrenocortical hyperfunction in cases of KW kidney at autopsy. There was an increase in weight of the adrenals by 24%, lipid vacuolisation in the zona fasciculata in 86% of cases and a greater incidence of adrenal adenomas. Experimental evidence from rabbits shows that administration of anterior pituitary extracts, and cortisone in healthy and alloxan diabetic animals results in the production of renal lesions considered similar to those of KW kidney. Becker (1952) reported a rise from 30% to 70% in the incidence of these lesions after cortisone injection when the animals were alloxan diabetic. Rosen (1956) reviewing the evidence for adrenal hyperfunction in diabetic retinopathy concluded that the failure to produce capillary microaneurisms consistently in experimental animals, and their infrequency in man after prolonged steroid therapy, constituted a weakness in the hypothesis.

Poulsen and Larsen (1961) have investigated the changes of intraocular pressure which accompany the fluctuation of blood sugar levels. Both hyperglycaemia and hypoglycaemia may produce a fall in the ocular tension. Hyperglycaemia due to insulin lack is a more potent factor than alimentary hyperglycaemia and may produce a 10% fall. Acute hypoglycaemia may result in a fall of as much as 20%. The variations are more marked in severe diabetics. It is argued that these changes put a mechanical stress on the walls of the retinal blood vessels depriving them of their normal support. Mooney (1963) reports two clinical observations in support of this idea. In a patient with mild diabetic retinopathy the second eye which was blind from glaucoma was free of retinopathy. Another patient with severe retinopathy was observed to have low ocular tension in association with vitreous hæmorrhage, which rose to normal as the hæmorrhage resolved.

A rise in the level of serum lipids is found in many diabetics. It increases in patients with retinopathy and is even higher in those with nephropathy, but as it occurs in other diseases unaccompanied by retinopathy it must be considered a non-specific change (Larsen, 1960). The same can be said of the protein-bound carbohydrate and hexosamine fractions which are increased in diabetic retinopathy. Ashton (1959) has drawn attention to the fact that none of these biochemical changes can be invoked

to explain the localisation of the lesions to the retina.

Treatment

The legion of treatments advocated at various times for this complication is a sure indication of the unsatisfactory results obtained, so much so that many consider the condition untreatable. A fundamental difficulty lies in deciding the criteria on which treatment may be assessed. Some of the manifestations of retinopathy, for example retinitis proliferans, are consequent on extensive injury to the tissues, whilst others, hæmorrhages and microaneurisms, are much closer to the primary lesion of diabetic retinopathy. Because the natural evolution of the retinopathy is slow it is important to look for improvement in those clinical manifestations which are close to the primary lesion, as the others may continue to progress under the momentum of the injury already inflicted. This applies particularly to retinitis proliferans which is a connective tissue reaction, and possibly also to exudates which are never seen in the absence of established retinopathy.

A comparison of the results of different workers is difficult because of the lack of uniformity in their criteria of assessment. Repeated estimation of the visual acuity which has the advantage of a close relationship to the amount of useful vision experienced by the patient, is unfortunately a poor guide to the progress of the retinopathy; in cases where vitreous hæmorrhage is occurring wide fluctuations are encountered in the visual acuity, irrespective of the trend of the disease. Changes in refraction, cataract, and intercurrent ocular disease can also upset the visual acuity. Joplin, Hill, Scott and Fraser (1962) have studied serial retinal photographs of selected areas of the retina, assessing them in terms of five components, hæmorrhages and microaneurisms, venous dilatation, new vessel formation, retinitis proliferans and exudates. Using a four-point scale of severity they were able to demonstrate the trend of retinopathy in treated and untreated cases. It is not possible to study the whole fundus by photography so Contreras, Field, Hall and Sweet (1962) preferred to document their cases by repeated fundus drawings made with the aid of the binocular indirect ophthalmoscope, affording a diagram of the whole fundus and vitreous but losing the accurate detail of the retinal photograph.

The natural history of diabetic retinopathy is very variable both in the rate of deterioration and the incidence of periods of inactivity,

sometimes of arrest. Beetham (1963) has observed spontaneous arrest for periods of 1-9 years in 10% of a group of patients with proliferative retinopathy who received no specific treatment for the complication. These observations cast grave doubt on the significance of treatment in isolated cases of improvement, and indicate the need for some form of control in any therapeutic trial relating to diabetic retinopathy.

Three lines of treatment will be discussed, pituitary ablation, anabolic steroids, and low fat diets; in addition light coagulation will be mentioned. Other methods of treatment have included the exhibition of vitamin B₁₂, rutin, lipotropic substances, and œstrogens but with little success. The impetus for pituitary ablation came from the observation by Poulsen (1953) of remission and eventual clearing of retinopathy in a woman who suffered from post-partum necrosis of the pituitary, with clinical Simmonds disease and increased sensitivity to insulin. Ablation can be produced by hypophysectomy (Luft, Olivecrona, Ikkos, Kornerup, and Ljunggren, 1955; Kinsell, 1957; Schimek, 1956; Javid, Gordon and Erickson, 1958; Vannas, Hernberg and Björkstén, 1959) performed transcranially or trans-sphenoidally; alternatively the pituitary stalk may be divided and a diaphragm inserted to prevent healing of the portal venous system (Contreras and others, 1962). Irradiation with a neutron beam (Sangalli, 1961), and implantation of radioactive Yttrium-90 seeds through a cannula passed across the top of the nasal cavity under radiographic control (Fraser and Joplin, 1961) are alternative methods. Intracranial surgery in diabetic patients is fraught with more risk than usual from thrombosis and infarction of the retracted lobes of the brain; for that reason the nasal approach is sometimes preferred. Surgical hypophysectomies produce complete ablation of immediate onset in the majority of patients. After an Yttrium implant the first sign of decreased activity is a sharp drop in the insulin requirement, usually manifest on the fifth day (Joplin and others, 1962). Irradiation from the cyclotron takes longer to act and is not free from risk of damage to surrounding structures. Stalk section like Yttrium implant produces a proportion of incomplete ablations, but present evidence though not conclusive suggests that there may be little difference in the effect on retinopathy of partial or complete ablation. Improvement in nearly all aspects of retinopathy was reported by Contreras and others (1962), but Joplin and others (1962)

found only dilated veins, hæmorrhages and new vessels favourably influenced. This series of patients has been followed and additional patients recruited; in 1963 Hill reported that about one-third of them showed improvement in respect of dilated veins, hæmorrhages and new vessels, none was worse; but retinitis proliferans deteriorated in half the cases and exudates showed little change. By contrast a comparable unimplanted group showed no significant change in respect of venous dilatation, hæmorrhages and new vessels. At a recent symposium held to consider the effects of hypophysectomy and adrenalectomy on diabetic retinopathy (Luft, 1962) most speakers reported arrest or improvement in about half their cases. Operative mortality was not serious but there was a considerable mortality in the years of follow-up due in many cases to renal failure. Gordon and Javid (1962) reviewed the metabolic effects of hypophysectomy and considered that patients could be maintained in the Houssay state for at least five years. Limited renal function was the major hazard.

Anabolic steroids have been given to counteract the changes in serum proteins occurring in diabetic retinopathy, a fall in serum albumin and a rise in the alpha-2 globulins which contain lipoproteins and mucopolysaccharides (Dardenne, 1961). These changes are considered to be due to the action of glucocorticoids, consequent on pituitary and adrenal hyperfunction. Dardenne has treated 48 patients for periods of eighteen months and longer with Decadurabolin and Orgabolin, following the effect with retinal photographs; 8 patients improved, 34 were stationary and 6 deteriorated. Saskin, Waldman and Pelnér (1951) treated 28 patients with testosterone propionate, and found that 11 showed no fresh hæmorrhages, 10 were improved and 7 unchanged after periods of two to six months. Valk (1960) reported a single case of improvement. The duration of these trials was too short to form an opinion about the effectiveness of treatment, and in the series of cases presented by Dardenne no mention is made of the criteria by which the results were judged.

The extent to which hard exudates are due to intracellular fat liberated by necrosis, or serum lipid infiltration, is uncertain (Van Eck, 1959), but of 10 patients on a low fat diet (20 grams a day) for an average period of one year exudates were reduced in 5 cases and slightly reduced in a further 3; vascular changes and hæmorrhages were uninfluenced. King, Dobree, Kok, Foulds and Dangerfield (1963)

treated their patients on a low fat diet to which unsaturated vegetable fats were added; there was a reduction of the total serum lipids and an improvement in exudates in 21 out of 26 cases. In a comparable group of untreated cases 11 improved, 4 were unchanged and 11 were worse. Unfortunately the disappearance of exudates left a permanent scotoma so that there was no significant improvement in vision.

Light coagulation of areas of active retinopathy (producing a controlled local coagulation necrosis by means of a high intensity light source, an effect similar to the natural phenomenon of an eclipse burn) has been advocated by Wetzig and Worlton (1963), and the preliminary results show moderate success.

The results of treatment are unsatisfactory though superior to comparable untreated groups; the management of patients must be assessed in this context. Pituitary ablation produces considerable general effects and requires careful replacement therapy with adequate medical supervision always available. It is likely to be superseded when the cause of retinopathy is better understood, but for the present should be considered when the retinopathy is severe and active but not too advanced, provided there is no renal impairment.

OTHER OCULAR MANIFESTATIONS

Incidence

An extensive survey of the ocular complications of diabetes was made by Waite and Beetham (1935) who examined 2,002 diabetic patients on the occasion of their first admission to hospital. The series included many new cases and some already under treatment for a period. To obtain an estimate of the incidence of these ocular conditions in patients not suffering from diabetes they examined concurrently another series of 457 patients also admitted to hospital for the first time. Mild chronic infections of the external eye were more common in the diabetic group and included squamous blepharitis and conjunctivitis from which staphylococci were often cultured; surprisingly meibomian cysts and styes were not common. Xanthelasma occurred more frequently in diabetics, but xanthoma diabetica was not encountered. Weakness of accommodation was found in 21% of patients under 50 years of age; it was never severe and was associated in 40% of the cases with a history of transient refractive changes suggesting that it was lenticular in origin. Evidence of depigmentation of the iris was found in 6% of the diabetic

patients as compared to 2% of the other group. Poor dilatation of the pupils following the instillation of mydriatics for routine examination was found in 4% of the diabetic cases, the patients having normal pupillary reactions. Argyll-Robertson pupils occurred in 2.8% of the diabetics, in half of the cases there was no clear indication of syphilitic origin. Iridocyclitis occurred with equal frequency in both groups, 1.3% of cases. Senile cataract was found to have a similar incidence in the two series of patients in all age groups. Amongst juvenile diabetics cataract was found in 4% of cases of which half were poorly controlled, it progressed at varying rates and once established was uninfluenced by diabetic control. Transient refractive changes were reported in 6% of patients. 7 male diabetic patients were found to have changes typical of tobacco amblyopia, but in no case was an affection of the optic nerve found specific to diabetes. Ocular muscle palsies occurred in 0.8% of the diabetic patients.

Leopold (1945) reviewed a series of 100 patients who had had 10 years careful diabetic management and compared his findings with those of Waite and Beetham (1935); he found little significant change save that the incidence of retinopathy had increased.

Changes in the Lens and Refraction

Because of the widely fluctuating blood sugar levels, and alteration in the state of hydration of the tissues, changes in the refraction of the eye are frequent in uncontrolled diabetes. A change towards myopia is usual in uncontrolled patients with a rapid swing towards hypermetropia when the blood sugar is brought under control. There is a diversity of opinion about the mechanism of these changes (Lawrence, Oakley and Barne, 1942; Duke Elder, 1949) though they appear to be osmotic effects acting on the crystalline lens. A change of 2-3 dioptres is usual but it may be exceeded; it is often astigmatic affecting one meridian more than another. With the onset of hypermetropia the patient may be considerably inconvenienced particularly when attempting to read, but it is seldom necessary to prescribe glasses as the changes are transient lasting only a week or two when the diabetes is adequately controlled.

Transient changes are seen in the crystalline lens of the eye in diabetic coma (Lawrence and others, 1942), due to the intense dehydration which also produces profound ocular hypotension, they disappear rapidly when the

condition is brought under control. In these cases the globe of the eye feels very soft to the fingers and with the ophthalmoscope opacities can be seen in the crystalline lens which take the form of wavy lines due to capsular folding, with vacuoles and clefts, and occasionally denser opacities. Transient lens changes have also been noted following the control of severe diabetes; they take differing forms. Lawrence (1946) reported two cases in which radial cortical opacities appeared and lasted 2-4 weeks. Diabetic cataract is a rare entity occurring bilaterally in young patients. Snowflake opacities appear in the anterior and posterior cortex under the lens capsule and progress to complete opacity sometimes within a few weeks; its incidence and relation to diabetic control have been noted. Senile cataract though no more common in the diabetic probably matures faster (Scott, 1953) so that the total incidence may be higher. In any event a routine urine test is essential in all cases of cataract, both for the detection of undiagnosed diabetes and to ensure that the disease is adequately controlled before operation. Both types of cataract can be removed surgically with reasonable prospects of useful vision provided the eye is otherwise healthy, especially free from new vessels on the iris and serious retinopathy. Post-operative hæmorrhage and iridocyclitis are more liable to occur in the diabetic patient and form the major hazards to successful cataract extraction (Nutt, 1953).

Changes in the Iris

Oedema and vesiculation of the pigment epithelium on the posterior surface of the iris results from infiltration of the cells with glycogen and their consequent degeneration. Ultimately the pigment is liberated and deposited on the structures bounding the anterior chamber of the eye, the posterior surface of the cornea and the anterior capsule of the lens. These deposits and the depigmentation of the iris can be detected with the slit lamp microscope. The gross thickening of the pigment epithelium is probably the basis of the poor dilatation of the pupil in response to mydriatic drugs which has already been mentioned.

The growth of new vessels on the surface of the iris is often associated with severe proliferative retinopathy; they are first seen on the anterior surface just beyond the pupillary margin, appearing as a dull red patch which spreads round the pupil and peripherally. New vessels also develop in the angle of the

anterior chamber at the same time; they are only visible by gonioscopy using a special contact lens, and block the filtration angle leading to haemorrhagic glaucoma. The term rubeosis iridis is given to this neovascularisation.

Diabetes does not influence the incidence of iridocyclitis (Waite and Beetham, 1935), and in a recent review of the concept of diabetic iritis Woods (1961) came to the conclusion that there was no form of iridocyclitis specific to diabetes, nor could the disease be considered an aetiological factor in uveitis.

Optic Neuritis

Skellern and Lockhart (1959) report 14 cases of optic neuritis in patients with uncontrolled diabetes. The onset was gradual and the condition bilateral in most cases, papillitis was observed in some cases and optic atrophy in others; a central scotoma or peripheral contraction of the field of vision was found. Control of the diabetes prevented further deterioration but only 3 patients experienced any improvement of vision. The condition was considered to be due to the toxic effects of diabetes on the optic nerve in susceptible subjects; the low incidence of neuropathy, present in only 3 of the cases, and the short duration of the diabetes were thought to differentiate it from neuropathic and vascular disturbances. Duke Elder (1940b) described the condition as of sudden onset, often bilateral, more common in males and showing a dense sharp-edged scotoma which was central, pericentral or cæcocal (that is, a loss of visual field centred on or around the fixation point, or lying between it and the blind spot); the prognosis was uncertain, rapid resolution or persistence with consequent optic atrophy might occur. Scott (1953) drew attention to the acknowledged sensitivity of diabetic patients to the toxic effects of tobacco as manifest by tobacco amblyopia, and agreed with other authors (Waite and Beetham, 1935; Walsh, 1947) in doubting the existence of a specific diabetic optic neuritis. In assessing the evidence it should be remembered that there are numerous causes of optic neuritis and some cases remain unassigned despite full investigation. The possibility of a genetic factor in some of these cases is suggested by the report

of primary optic atrophy in two patients, male and female siblings with longstanding diabetes unsatisfactorily controlled (Tunbridge and Paley, 1956).

Ocular Palsies

Diabetic ophthalmoplegia affects the third or sixth cranial nerves, rarely the fourth (King, 1959), and often occurs against a background of previous cranial monoplegia which has recovered spontaneously without further complication. It is a complication of middle aged patients with controlled diabetes or mild unrecognised disease; peripheral neuropathy and retinopathy are not necessarily associated. Goldstein and Cogan (1960) reviewed 22 cases of third nerve palsy considered after investigation to be due to diabetes, and compared them with 39 other cases due to various causes. The onset of diabetic ophthalmoplegia was sudden, often preceded or accompanied by a homolateral headache, closely resembling the clinical presentation of an intracranial aneurism. Paralysis of the external muscles was partial or complete but the pupil was usually spared and internal ophthalmoplegia occurred in only 5 cases, being incomplete in 2. By contrast 29 out of the 39 other cases which included several due to aneurism, were affected by internal ophthalmoplegia. All the diabetic cases recovered, the time varied from six days to four months, but repeated attacks were found in several patients.

Other Complications

It remains to mention briefly two other complications of diabetes: subjective visual symptoms in hypoglycaemia, which take various forms, for example blurring of near vision, diplopia or luminous scotomata, which are usually constant for each patient; and the rare condition of lipæmia retinalis seen when the fat content of the blood is grossly raised in severe untreated diabetes, so that the retinal vessels present a peculiar milky pallor turning to pink near the optic disc.

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