

OCULAR COMPLICATIONS OF DIABETES MELLITUS*

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A GENERAL review of the more important aspects of diabetes mellitus is desirable before proceeding to a consideration of the particular problem of the ocular complications.

Diabetes mellitus, already a common disease, is likely to become more common in the future. It has been estimated that in the United States of America there are about 1 million diabetics and probably another million undiscovered, and in the United Kingdom the number has been variously estimated at different times from 33,000 (Stocks, 1949) to 200,000 (Joslin, and others 1946). In Cardiff there are two diabetic clinics, one at the Royal Infirmary, and the other at the City Council Health Centre. Approximately 1,200 attend these clinics, and of these, six hundred reside within the boundaries of the city, which, with an estimated population of 250,000, gives an incidence of 240 cases of diabetes per 100,000 of population, this figure being comparable with that obtainable in other parts of the country. No fewer than 268 new patients were seen during 1952, and approximately six to eight new patients seek advice each week. These figures refer only to those attending the clinics, and there must be many others who do not attend or who are as yet undiscovered.

The disease is becoming more common for a variety of reasons. Firstly, it is a hereditary disease and is transmitted as a Mendelian recessive. Secondly, since the discovery of insulin, there has been an increase in the fertility of diabetics, a reduction in the incidence of maternal mortality, and an improvement in the foetal survival rate. It has been estimated, for example, that for every 282 pregnancies, there is one diabetic pregnancy, whilst the maternal mortality has been reduced to between 2 and 9 per cent. (Gilbert and Dunlop, 1949). Thirdly, diabetics are living longer and, if properly controlled, may live almost as long as non-diabetics. This is mainly due to insulin therapy, but improved dietary control and the advent of chemotherapy, antibiotics, and anticoagulants play an important part. It has been estimated that a child developing diabetes mellitus at age 10 had an expectation of life of 2·6 years in 1922 as compared with one of 39·8 years in 1938; comparable figures for a young adult are 6·3 years in 1922 and 27·6 years in 1938.

Factors influencing the Development of Diabetes.—Although the probable cause of diabetes mellitus is a degeneration of the beta cells of the islets of Langerhans in the pancreas, the exact cause is not known; there are, however, a number of factors which influence its development, and a proper appreciation of these should

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help to reduce the incidence of the disease and consequently of the development of retinopathy. These factors are:

(1) *Hereditary Transmission*.—Diabetics who marry other diabetics or marry those with a family history of the disease, should be warned of the probability or possibility of their offspring acquiring the disease, or of transmitting the strain.

(2) *Infections and Sepsis*.—These usually exert a temporary adverse influence upon the course of the disease, and in many cases act as a precipitating factor in its development. They are of special significance in causing diabetic retinitis, as shewn by Ballantyne (1946), who found them a factor in 35 out of 561 cases of diabetic retinopathy.

(3) *Obesity*.—It is firmly established, both by life insurance company statistics and by clinical studies on both sides of the Atlantic, that this is a most important factor in the middle-aged and elderly, particularly when there is a predisposition to the disease. There is no doubt that diabetes may be avoided in at least a proportion of the population if it is appreciated that consistent overeating will result in a sustained increased demand for insulin, which may so over-tax the pancreas that it will fail and result in the development of diabetes.

(4) *Disorder of other Endocrine Glands*.—This, especially in the thyroid and pituitary glands, may be associated with diabetes mellitus, which usually responds favourably when the other endocrine disorder has been corrected.

(5) *Tobacco*.—Elderly diabetics are said to be especially liable to develop tobacco amblyopia (Joslin and others, 1946). There is no evidence that diabetic retinopathy is related to the blood level of cholesterol, urea, or calcium, or to the presence of acidosis or ketosis (Lawrence, 1951; Ballantyne, 1946).

Diagnosis.—Although the classical symptoms of the disease usually cause the patient to seek advice, in some the discovery of diabetes may be entirely fortuitous during routine testing of the urine for various purposes. When the presence of the disease is suspected, it is usually sufficient to obtain a single blood sugar estimation to establish the diagnosis, but if this result is inconclusive, a full glucose tolerance test must be obtained.

Clinical Types

Mild Diabetes.—The disease is usually mild when it appears for the first time between the ages of 40 and 65. In such cases, it usually causes pruritis, retinitis, gangrene, neuritis, and loss of weight, whilst ketosis and coma are practically unknown. The patients are usually insulin sensitive, and either need very little insulin or respond well to dieting alone.

Severe Diabetes.—Although the disease in a severe form may affect all ages, it is especially liable to occur in those under the age of 20 or over 65 years. The classical symptoms of thirst, polyuria, lethargy, and loss of weight are usually present, and if they are untreated, ketosis and coma result. Such patients are usually insulin resistant, and are rarely controlled without large doses.

Clinic Arrangements in Cardiff

It must be accepted that control of the disease and care of the diabetic patient are essential. Whilst this can be effected in most patients by attendance at a clinic, all young diabetics and those with ketosis should be treated first in hospital.

In Cardiff we have the active support of the City Council, who provide and maintain an "after care" clinic to which patients are referred after investigation and

stabilization at the hospitals. This excellent arrangement not only ensures periodic supervision of the patient, but saves appreciably the occupancy of hospital beds by diabetics. The clinic is supervised by a consultant physician and the Medical Officer of Health, assisted by a registrar, dietitian, health visitors, chiropodist, and cookery demonstrators. A most valuable feature of the service is the domiciliary contact by the health visitors, who thus ensure regular attendance at the clinic of would-be defaulters, and who give valuable advice to those in difficulty.

Control by Diet and Insulin

In the obese diabetic, the aim should be a reduction in weight by means of a low calorie diet to the calculated ideal weight for the patient. The very obese should be given a 1,000 calorie diet, the less obese a 1,500 calorie diet, containing about 120–150 g. carbohydrate each day. As many patients will find this regime difficult to follow, it is often desirable to prescribe a supportive drug, the most suitable being dextro-amphetamine sulphate 5–10 mg. before breakfast and before lunch. Although this drug will not of its own accord cause a loss of weight, it will enable the patient to control the demands of his appetite, and will remove depression and fatigue, and promote physical and mental alertness. It is relatively non-toxic and is safe to use except when there is a history of coronary arterial disease or when severe anxiety or insomnia are present.

It is a mis-application of treatment to prescribe insulin initially to overweight patients, for experience shows the great importance of reducing weight, and the administration of insulin will promote an increase in weight. Insulin therapy will be required for all patients with severe diabetes, particularly the young and elderly, and in those who are underweight and have definite symptoms or ketosis. A diet suitable for the patient's requirements is prescribed individually, taking into account his particular circumstances and tastes, and instructions are given on food exchanges, general care of the health, and the technique of insulin administration. In most cases a combination of soluble insulin and protamine zinc insulin is prescribed, but in the more severe type, or when meals cannot be taken regularly, it is preferable to employ soluble insulin twice or thrice daily. The dose will be a matter for precise assessment in each individual and will require variation from time to time.

If coma threatens, a search for a focus of infection should be made, solid food should be replaced by 3-hourly liquid feeds, each of about 24 g. carbohydrate, the urine should be tested every 3 hours, and soluble insulin given at these times in doses determined by the amount of sugar found in the urine.

Surgery and Choice of Anaesthetic

When a local anaesthetic is used, the normal routine should not be changed. If an anaesthetic of short duration is required, very little alteration need be made, but it is important to give the usual dose of insulin with an additional 50 g. carbohydrate in liquid form 2 hours before the operation. In major surgical procedures, it is wise to delay the event if possible till ketosis has been abolished. The general principle should be to maintain the normal routine for as long as possible and to give 50 g. glucose with the usual dose of soluble insulin 2 hrs before the operation. Afterwards, an intravenous drip containing 5 per cent. glucose in saline should be set up and the regime recommended for the pre-coma case instituted. The normal routine should be resumed as soon as possible.

Anaesthetics that induce vomiting or are toxic to the liver should be avoided. Thus ether and chloroform are not suitable, whilst thiopentone, nitrous oxide and oxygen, and cyclopropane are suitable.

Diabetic Retinopathy

A detailed consideration of the changes seen in diabetic retinopathy must be left to others more competent than I, and my remarks here will be confined very largely to general observations. It is disappointing for the physician to save young diabetics from coma and subsequently to help them to maintain a good standard of physical health only to find that years later they develop serious degenerative vascular diseases of which retinopathy is a very important and only too common example. It is not too much to claim that its prevention is the most important and challenging problem in the management of diabetes. Ocular complications are frequent and distressing and are becoming more common because of the increasing longevity of diabetics. Formerly not seen in the young because they succumbed to the disease at an early age, it now affects them in middle life or later. Apart from the humanitarian aspect, it is also an important economic problem, particularly when one considers that diabetics are often above average in intelligence, and because of their affliction are influenced to take up occupations of a clerical, professional, or skilled nature. It is particularly distressing that retinopathy is often seen even in those whose cases are classified as mild and well-controlled. It thus follows that it is all the more important to concentrate on prevention, paying attention to the factors known to influence the development of diabetes (*e.g.* heredity, obesity, sepsis, hyperthyroidism) and giving advice on their avoidance whenever possible.

Statistics show that diabetic retinopathy usually appears in those with long-standing diabetes, 10, 15, 20, 25 years, or more after the onset of the disease. The highest incidence thus falls in the middle-aged or elderly, although it is sometimes seen in the young. The proportion of diabetics affected varies according to age group, a reasonable average being about 30 per cent. of all diabetics. Higher proportions are found in older people; for example, retinopathy is found in 40 to 50 per cent. in the age group 60–70 years, and some writers claim an incidence of 70 and even 100 per cent.

Many claim that recent advances in treatment do not protect against the development of retinopathy, and that it is found as frequently in mild and clinically controlled cases, even in those taking insulin, as in severe or uncontrolled cases. These observers claim that what matters most is the duration of the diabetes, and that insulin has no influence in preventing the development of retinopathy (Saskin and others, 1951; Ballantyne, 1946). There are others, however, who maintain that proper and sustained attention to diet, regular supervision, and control of hyperglycaemia and glycosuria have an important influence in preventing the development of retinal changes. (Lawrence, 1951; Scott, 1951; Wilson and others, 1951; Joslin and others,

1952). Joslin, in particular, states that if young diabetics are taught properly how to manage their disease, complications need never develop, and to further this object he has advocated the construction of suitable diabetic camps or homes or special hospitals with proper facilities. As explained above, a special "after care" clinic supported by health visitors, etc., has been fulfilling this important function in Cardiff. Whatever one's personal views on the influence of treatment, it would be foolish to ignore the importance of proper and adequate control of diabetes, particularly with regard to diet.

It is necessary to refer to the influence of hypertension in relation to the development of retinopathy. In general it may be stated that most authorities agree that diabetic retinopathy is independent of and distinguishable from the effects of arteriosclerosis and hypertension (Ballantyne, and Loewenstein, 1943; Ballantyne 1946; Lawrence, 1951; Scott, 1951; Bedell 1939; Joslin and others, 1946). It is well recognized, however, that in the later stages retinal changes characterized by hypertension may be superimposed on those due to diabetes, and that in advanced cases it may be impossible correctly to apportion the blame.

Retinitis proliferans is known to occur as a late complication of diabetic retinopathy in long-standing cases, the retinal changes being accompanied by severe damage to the kidneys and also hypertension. Similar pathological lesions are found in the retinae and glomeruli of the kidneys. In retinitis proliferans, the prognosis is hopeless as regards vision and is grave as regards life, the majority affected dying at an early age from anaemia or cardiac failure. The disease is associated with albuminuria in two-thirds of the cases and with arteriosclerosis and hypertension in the majority. Although many young diabetics are affected, more than 50 per cent. of cases occur after 50 years of age.

Kimmelstein-Wilson disease is also one which occurs in long-standing diabetics, and is also characterized by renal and retinal lesions resulting in early death from renal or cardiac failure, and also in blindness. An associated lesion is an intercapillary glomero-sclerosis.

Apart from these two specific diseases, diabetic retinopathy may be complicated by the onset of renal failure from other causes or by hypertension and arteriosclerosis.

The fundus picture in diabetes is progressive and the prognosis with regard to vision in diabetic retinopathy is bad in the extreme. (Ballantyne and Loewenstein, 1943; Ballantyne, 1946). There are some, however, who claim a more favourable prospect with the exception of advanced degrees of retinitis proliferans and Kimmelstein-Wilson disease (Lawrence, 1951; Whittington, 1951; Joslin and others, 1946). It is generally agreed that the fundus changes are no guide to life expectancy.

As already indicated, I will leave the detailed consideration of the fundus picture to others, except to mention briefly that the whole course of development, beginning with the appearance of micro-aneurysms, followed by dot

and blot haemorrhages, wax exudates, and phlebosclerosis, and later by haemorrhages in the vitreous and destruction of the retina, represents one progressive process. The exact cause is a matter for speculation, but since diabetes is a common factor in all cases it seems logical to conclude that some toxic change peculiar to this disease must play an important part.

It is claimed that rutin has a beneficial effect upon retinal haemorrhages (Levitt and others 1948), but in several cases in which this treatment has been tried in our clinics, the results have not been at all impressive. It has also been claimed that testosterone therapy will produce an unequivocal improvement in 30 per cent. and improvement in another 40 per cent. of cases (Saskin and others, 1951); I have had no personal experience of this form of therapy, and the absence of any further reference to it in the literature suggests that it has not been received with marked favour.

In addition to the retinal changes occurring in diabetes, cataracts often develop in long-standing and especially in untreated cases. These may be caused by the high sugar content of the eye, but on the other hand, the incidence of cataracts in non-diabetics is quite as high as in diabetics. Temporary changes in accommodation causing either myopia or hypermetropia may result from changing refraction due to varying sugar content, particularly in those receiving insulin.

Retrobulbar neuritis and diplopia occur occasionally, and more rarely lipaemia retinitis, optic tract lesions, optic atrophy, and paralysis of the ocular muscles may be encountered.

Present Series of Cases

There are about 1,200 diabetics attending the clinics in Cardiff, and for the purpose of this investigation, one hundred of these patients were taken at random and submitted to a detailed examination with special reference to fundus changes.

An analysis of the fundus appearances is tabulated in Table I, from which

TABLE I
FUNDUS APPEARANCES IN 100 UNSELECTED
CASES OF DIABETES MELLITUS

No view of either fundus	7
Non-diabetic abnormalities	3
Normal	27
Slight vascular changes not definitely diabetic	29
Diabetic retinopathy	34

it will be seen that 34 cases were considered to have diabetic retinopathy; as no view of the fundus could be obtained in seven patients, this gives an incidence of 37 per cent. The detailed changes observed in the fundi of these 34 patients are recorded in

Table II (overleaf), which shows the appearances to be fairly typical of diabetic retinopathy in 25 patients, and rather more typical of retinitis proliferans in nine patients.

The correlations between the clinical findings and the occurrence of diabetic retinopathy in the whole group of 93 patients in whom a good view of the

TABLE II
CHANGES SEEN IN FUNDI IN 34 CASES OF DIABETIC RETINOPATHY

Punctate haemorrhage	without vascular changes	9
	with slight to moderate venous changes	2
Hard exudates	with hard exudates	2
	with exudates and vascular changes	12
Large haemorrhage with moderate vascular changes	with gross vascular changes	1
	with gross vascular changes and large haemorrhage	3
Reflexes in knees and ankles absent	without vascular changes or large haemorrhage	1
	without exudates	1
Family history of disease	with exudates	3

fundus was obtained and an analysis of the 34 cases with diabetic retinopathy is given in Table III, from which some interesting facts emerge:

TABLE III
CORRELATION OF CLINICAL GROUPS WITH DIABETIC RETINOPATHY

Clinical Group	Total No. of Patients	Diabetic Retinopathy Present		
		No. of Patients	Percentage of Total	Percentage of 34 Patients with Retinopathy
Good view of fundus	93	34	37	100
Age at examination	Under 40 years	18	1	3
	40 - 60 years	37	10	30
	Over 60 years	38	23	67
Age at onset of disease	Under 40 years	29	5	15
	40 - 60 years	45	18	53
	Over 60 years	19	11	32
Duration of disease	Under 10 years	69	23	67
	10 - 20 years	18	8	24
	Over 20 years	6	3	9
Disease well controlled	Yes	51	21	62
	No	42	13	38
Blood pressure	Normal	44	9	26
	Moderate (170/90)	25	9	26
	Severe (200/105)	24	16	47
Albuminuria present	...	16	10	30
Reflexes in knees and ankles absent	...	14	11	32
Family history of disease	...	28	10	34

(1) The incidence of diabetic retinopathy in an unselected group of diabetic patients is 37 per cent.

(2) The incidence of diabetic retinopathy increases markedly with increasing age at the time of examination.

(3) A similar but less striking trend is noted when incidence is related to age at onset.

(4) When the incidence of diabetic retinopathy is related to the duration of the diabetes mellitus it is found to be very little higher in the longest group than in the shortest. When the duration of the disease is analysed in the 34 patients with diabetic retinopathy, no less than 67 per cent. had had the disease for less than 10 years, only 9 per cent. having had it for 20 years, and the remaining 24 per cent. falling into the 10-to-20-year group. These figures indicate that the actual duration of the disease is not so important as might be thought.

(5) There is a higher incidence of diabetic retinopathy in patients with well controlled diabetes than in those not so well controlled.

(6) The incidence of diabetic retinopathy increases with a rise in blood pressure.

(7) Of patients with albuminuria, no less than 62 per cent. have retinopathy, and the incidence of albuminuria amongst those with retinopathy is 30 per cent.

(8) Of those with absent reflexes in the lower limbs, 71 per cent. have retinopathy, and in 32 per cent. of 34 patients with retinopathy lower limb reflexes were absent.

(9) The incidence of retinopathy was 34 per cent. amongst those with a family history of diabetes, and 30 per cent. of patients with retinopathy had a family history of diabetes.

Summary

In the development of diabetic retinopathy, the age of the patient is what matters most, the incidence of this complication being highest in the oldest age group whether the age is calculated from the time of examination or from the time of onset of diabetes. High blood pressure, albuminuria, and neuropathy are commonly found in cases of diabetic retinopathy, and, as might be expected, in the unselected cases, the incidence of retinopathy is highest amongst those showing these abnormalities.

The duration of the disease is of some importance, but there is little variation in the incidence of retinopathy in the under-10-year group as compared with the 10-to-20 and over-20-year groups of unselected patients; the surprising fact emerges, however, that, of those with retinopathy, no less than 67 per cent. were found in the under-10-year group as compared with 24 per cent. in the 10-to-20-year group and 9 per cent. in the over-20-year group.

The most disappointing feature of this analysis is that the incidence of retinopathy is higher in the group of controlled diabetes than in the less well controlled group.

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