COMMUNICATIONS

DIABETIC RETINOPATHY—A CHALLENGE*

BY

ALAN J. MOONEY

Dublin

I AM very conscious of the fact that, being an ophthalmologist, I have only a superficial knowledge of diabetes mellitus and also that, not being associated with a diabetic clinic, I have had only limited opportunities of studying its retinal complications. Any observations I make will, therefore, be open to the criticism that they would not form the basis of a statistical analysis. For these shortcomings I ask your indulgence.

The assessment of individual cases can, however, be rewarding. This was emphasized by Poulsen's observation that severe retinopathy regressed in a diabetic who developed hypopituitarism post partum. It was this isolated case that led to the various forms of pituitary ablation as a form of treatment for retinopathy. With this in mind my efforts have been directed towards the careful study of a few cases selected from a series of 250, together with a superficial survey of the remainder, covering a 2-year period.

"I often wonder why physicians send me their patients with diabetic retinopathy. What can I do for them?"

This comment was recently made to me by an ophthalmologist of international repute and truly demonstrates how little we know about this complication of diabetes. It is because of retinopathy that we have assembled here to-day in the hope that we may make some advance towards finding a cause of this complication and instituting some prophylactic therapy. Since the discovery of insulin the survival price in diabetes has been offset by the development of long-term vascular complications. Owing to recent advances in treatment, the diabetic birthrate is increasing and, since heredity is such a potent influence, the diabetic population is sure to increase. Moreover, the increased expectation of life in diabetics also adds to their numbers. It is clear, therefore, that, within this decade, diabetic retinopathy will become a problem of increasing magnitude. In our time the pattern of blind statistics in these islands has changed; we have seen blindness from trachoma, retrolental fibroplasia, and ophthalmia neonatorum disappear. The ocular manifestations of certain general diseases, such as tuberculosis and syphilis, are

* Presidential Address at the Joint Meeting of the Irish Ophthalmological Society and the British Diabetic Association held in Dublin, April 25 to 27, 1963.

rare and, thanks to modern neuro-surgery, the visual disorders that accompany brain tumours can, in many cases, be dealt with effectively. On the other hand, the increased ageing of the population brings with it the survival of those who, by heredity or other causes, develop diseases which may eventually lead to blindness. Among these are diabetic retinopathy and glaucoma. I think most Irish ophthalmologists would regard glaucoma as the major cause of unpreventable blindness in the over-40 age group, and there is no subject that has involved more research or caused more therapeutic failures. Notwithstanding, there has been no major advance in dealing with glaucoma for over 40 years. This period is coincidentally significant because over 40 years ago very few diabetics survived long enough to develop retinopathy, but their longer lives are now making this condition a problem in our generation.

The importance of diabetic retinopathy as an ocular problem is emphasized by the fact that 97 per cent. of diabetics develop it if they live the normal span. In Denmark diabetic retinopathy heads the list of causes of blindness with 22·8 per cent. Moreover, of the 874 certified blind in the Commonwealth of Massachusetts between July 1, 1958, and June 30, 1959, diabetes accounted for 148 (17 per cent.), thereby exceeding all other groups. In Great Britain, amongst the registered blind in the under-60 age group in 1962, diabetic retinopathy formed 11·3 per cent. against 4·6 per cent. for glaucoma. I could give other figures that would demonstrate the serious nature of the problem that confronts us and which makes me feel that inadequate attention has been devoted to this blinding disease compared with other common causes of blindness, such as glaucoma.

Diabetes and Glaucoma

Frequent mention of diabetes and glaucoma in the same context has drawn my attention to certain mutual features:

- (1) Both diabetes and glaucoma have a strong hereditary background.
- (2) The majority of both diseases are found in the over-40 age group and affect a somewhat similar percentage of the population. Half of this number, incidentally, are unaware of the fact that they are suffering from a disease.
- (3) Emotional stress is an aggravating factor in each condition, resulting in diurnal variation of the blood sugar in diabetes and increased intra-ocular pressure in glaucoma.
- (4) In the over-40 age group each disease is characterized by an insidious onset, and irreversible signs are often present when the patient first consults a doctor.
- (5) We hope, by detecting each condition before it becomes overt, to prevent its further progress. Efforts have been made, therefore, to organize screening tests in all persons over 40 years of age, and especially those with a

family history of either disease. Frequently it is considered desirable to follow this up by provocative tests (glucose tolerance in diabetes and water-drinking and other tests in glaucoma) and should these prove positive the patient may be kept under observation indefinitely. It has been suggested that a special centre may exist in the hypothalamus which is primarily responsible for the onset of glaucoma, and Prof. Young has postulated the theory that the original cause of diabetes might be a temporary overaction of the pituitary on the adrenals. These views, coupled with the use of pituitary ablation for diabetic retinopathy make me feel that perhaps, some day, diabetic retinopathy and a glaucoma may be absorbed into the field of neuro-ophthalmology with the hypothalamus as the focal point.

These observations may not be of significance but they suggest that clinical research on diabetic retinopathy and glaucoma might well be effectively organized from the same department. Indeed one might go further and envisage a travelling unit, operated on similar lines to Mass Radiography. By this means screening tests for both diabetes and glaucoma could be carried out on all persons over 40 years of age. While appreciating the psychological objections, I feel that this would be an effective method of detecting both pre-diabetes and pre-glaucoma, in the reasonable hope of minimizing the risk of long-term complications of either disease.

While on the subject of glaucoma, it is of interest to mention that, in my experience, the presence of diabetic retinopathy in a patient with glaucoma is a rare occurrence. This may, of course, be due to the law of averages, but more significance may be attached to this observation as a result of the findings in the following case.

A man aged 64 years had been a mild diabetic for 7 years. The fasting blood sugar was normal but he had a diabetic glucose tolerance curve. He was well controlled with Rastinon and diet and subsequently by diet alone. The right eye had no glaucoma, but the left eye was blind from glaucoma. The non-glaucomatous eye showed mild retinopathy with a large haemorrhage below the inferior temporal vessels. The eye which was blind from glaucoma was free of diabetic changes.

Some significance may well be attached to the fact that the retinal changes were present in the eye with the lower tension. Is it possible that the increased intra-ocular pressure in the other eye, by compressing the capillaries and venules, retarded the development of retinopathy?

Diabetic Retinopathy

It appears to me that there are two main types of retinopathy. The first is the common slowly-progressive variety, associated primarily with micro-aneurysms, which subsequently advance into the other grades so clearly described by Ballantyne (1946). In this type the arterio-venous ratio may be slightly increased in the later stages, but there is no marked irregularity of the retinal veins and the lesions are concentrated in the perimacular zone while

sparing the fovea centralis. It can be many years before the vision is affected, if indeed it ever is. The intra-ocular pressure remains normal. The second variety, fortunately less usual, is marked, even in the early stages, by engorgement and irregularity of the retinal veins, with numerous "dot" and "blot" haemorrhages along their course. Neovascularization develops and subsequently vitreous leakages occur. This is the serious type which, subject to occasional remissions, steadily progresses with visual deterioration and subsequent blindness. It is my experience, in the few cases of this kind that I have studied, that the intra-ocular pressure varies between normal and subnormal, the latter synchronizing with deterioration in the fundus and vitreous haemorrhage. This supports the view expressed by Poulsen and Larsen that variations in the intra-ocular pressure may be a pathogenic factor in the production of venous dilatation, a condition which is most marked when the diabetes is out of balance. The following case illustrates this point.

A woman aged 31 years had been a diabetic for 18 years. Control had been poor initially but for the past 3 years had been usually good, during which time the insulin dosage varied between 48–64 units "lente". She had severe retinopathy with marked increase in the arterio-venous ratio. The intra-ocular pressure remained at 20 mm. Hg (Schiötz) until 15 months later when I was called to see her on account of a sudden deterioration in vision. I found that she had bilateral vitreous haemorrhages with an intra-ocular pressure of 14 mm. Hg; subsequently the haemorrhage cleared and the tension returned to 20 mm. Hg. Recently, the fundus picture became worse than when first seen and it is now only a question of time until the patient goes completely blind.

Is it possible that in this case the subnormal intra-ocular pressure had the reverse effect of the increased tension in the previous one?

If the answer is in the affirmative, this rather supports Bloodworth's theory that "microaneurysms and haemorrhages are due to the capillaries losing the support usually accorded by the degenerating nervous elements, the weakened capillary wall expanding into a thin-walled aneurysm". Periods of poor diabetic control leading to glycosuria and osmotic diuresis could cause a reduction in the water content of the eye. The ensuing hypotension might well accentuate the lack of support for the retinal veins, thereby predisposing to vitreous haemorrhage.

A statistically significant increase in the intra-ocular pressure in normal eyes has been reported from the use of both topical and systemic steroid therapy. As a prolonged course of the latter would not appear to be justified in diabetes, a trial is taking place with topical steroids in severe low tension retinopathy, but it is too early yet to evaluate the results. It would appear, therefore, that a prospective study with regular measurement of the intra-ocular pressure over a period of years in order to see if phases of low tension are related to deterioration in severe retinopathy might produce valuable information.

It is for this severe type of phleboopathy that hypophyseal ablation has been recommended. When contemplating this procedure one has to balance

the possibility of visual improvement against the risk of post-operative complications, together with the life sentence of replacement therapy. This procedure cannot be undertaken lightly and certainly not without very careful consideration of the possible after-effects. On the other hand, to observe the patient going blind, without making any effort to prevent it, is a grim prospect bringing despair to the patient and doctor alike. If, because they are not yet fully evaluated, one cannot recommend any form of pituitary ablation, generous appreciation must be shown of those pioneers who have indicated what may, some day, be achieved by conservative therapy.

There are two factors which, in the opinion of many, influence the development of retinopathy. The most generally accepted is that the diabetes *must be present for at least 10 years*. This may be true, but it is difficult to prove in cases wherein retinopathy is the presenting sign, the patient being symptom-free. The following cases illustrate this.

A woman aged 65 years came to my out-patient department because she had lost her reading glasses. Her visual acuity with correction was normal in each eye for distance and near. She had a few microaneurysms in the peri-central zone of each fundus. She was free of diabetic symptoms but had a heavy glycosuria and a fasting blood sugar of 300. Control was easily effected by means of Diabinese and diet. Notwithstanding the fact that her married daughter, aged 32 years, was actually a diabetic, this patient was unaware that, possibly for some years, she had been similarly affected.

A man aged 70 years also came to see me for a change of reading glasses. His visual acuity with correction was 6/18 in the right eye and 6/5 in the left. He had well-marked bilateral diabetic retinopathy, including a haemorrhage at the right macula, and he was also hypertensive but had no diabetic symptoms. Biochemistry, however, showed well-established diabetes which was rapidly controlled with 20 units soluble insulin morning and evening. It is interesting to speculate how long the diabetes had been present in *this* case.

The recognized view is that retinopathy is present in the large majority of long-term diabetics, but many cases such as the following can be produced to disprove this.

A man aged 50 had had diabetes for over 40 years. His occupation demanded his presence at numerous public dinners and other social functions and for this reason control had been haphazard for many years, yet I was unable to find a single microaneurysm in either fundus. It may be of significance to mention that his treatment had been meticulous in the early years of his disease and that he had always been on soluble insulin.

A woman aged 44 years had been a diabetic for 31 years. Control had been poor for many years with frequent hypoglycaemic attacks and periodic ketosis. No serious effort had been made by her to observe the dietary restrictions and she visited doctors only for complaints unconnected with her diabetic state. Notwithstanding, a fundus examination showed a normal arterio-venous ratio and I could find only one microaneurysm. In this case also therapy had been strict in the early stages when she had been on soluble insulin twice a day, but more recently she had been on a mixture of 30 "ultra" and 30 "semi-lente".

Numerous instances can be produced to show that rigid control is not the complete answer, while the foregoing cases clearly demonstrate that there is

some factor other than the long-continued presence of diabetes which influences the onset of retinopathy. Furthermore, the impression that patients on soluble insulin are less likely to develop retinopathy may be partly true but cannot be accepted without reservation, having regard to the frequency of retinopathy before the introduction of the long-acting insulins. The effect of diet, with particular reference to the use of vegetable oils, has been carefully evaluated by workers in this field. Many other factors, such as sustained ketosis, frequent hypoglycaemia, the age of the patient, hypercholesteraemia, and excessive weight, have all been suggested as factors which may influence the onset of angiopathy. Statistical surveys have failed to pinpoint any single feature which determines the presence or absence of retinal changes in diabetic patients, although some of those just mentioned appear to play an aggravating role.

Para-amino Salicylic Acid (PAS) in Diabetic Retinopathy

In a series of 250 cases examined during the past 2 years, two are of particular therapeutic interest, because they suggested a form of treatment which might have a beneficial effect on diabetic retinopathy.

A male student aged 20 years, first seen 2 years ago, had been a diabetic all his life and, for the previous 9 months, had been treated for pulmonary tuberculosis with streptomycin, INAH, and PAS. His visual acuity was 6/24 in each eye, and there was a small bilateral central scotoma for 5/2000, *red*. Fundus examination showed mild swelling of each disc and marked engorgement and aneurysmal dilatations of the retinal veins. There were numerous microaneurysms, "dot" and "blot" haemorrhages, and lipid deposits. The blood pressure was 120/80 and the fasting blood sugar 130. He was on 24 "lente" and 12 "semi-lente". Hypoglycaemic episodes were frequent. The presence of an intracranial space-occupying lesion was excluded. At this time the patient was treated with PAS only. The fundi steadily improved and are now normal with full visual acuity. The ophthalmoscopic findings in this case presented unusual features, but the changes were predominantly diabetic in appearance. The improvement was remarkable and it is of interest to speculate whether it could have been associated with the use of PAS.

A man aged 39 years, a diabetic of 14 years' duration, was first seen 2 years ago. He had developed pulmonary tuberculosis 6 years previously and while he was under treatment for this the diabetes was poorly controlled. He had gross bilateral retinopathy and there was a large vitreous haemorrhage in each eye. The tuberculosis cleared up after 12 months' treatment and he was subsequently maintained on PAS with 40 "soluble" and 40 P.Z. in the mornings. With the exception of frequent insulin reactions when at work he feels very well. The visual acuity has improved in the right eye from hand movements to 6/5. There is considerable fibrosis in each vitreous but no marked retinopathy, just a few microaneurysms in each fundus.

The same query arises in both these cases: was the disappearance of active changes due to PAS? As a result of our experience in these two cases I have tried a few patients on a prolonged course of Pasade, but it is too early yet to assess the results. In the following case of exceptional interest a patient with diabetic retinopathy showed marked improvement on PAS therapy.

A man aged 29 years had been a diabetic since he was 5 years old. Control had been poor about 3 years ago and shortly afterwards he developed eye symptoms. When he was first seen a year ago his visual acuity with correction was 6/12 in the right eye and 4/60 in the left, which had a large vitreous haemorrhage. The intra-ocular pressure was 14 mm. Hg (Schiötz) in each eye. Pasade was prescribed and in 6 weeks the vitreous had cleared and one could now see that there was gross engorgement and irregularity of the retinal veins with massive haemorrhages, some of which were pre-retinal, along their course.

3 months later a remarkable improvement had taken place in both the haemorrhagic condition and in the venous calibre, and the tension in each eye was 23 mm. Hg, but 2 months later he developed bilateral vitreous haemorrhage with visual deterioration and the tension fell to 12 mm. Hg in each eye. Recovery took place again and the visual acuity improved to 6/9 in the right eye and 6/12 in the left, with tension 20 mm. Hg in each eye.

Recently, however, following a severe respiratory infection, the fasting blood sugar rose to 400 and the blood urea to 85, and this was followed by an increase in vasoproliferation in the left eye, but the retinal veins maintained their improved appearance.

As a contrast we have had experience of the mild type of retinopathy in which both objective and subjective improvement followed a 9 months' course of Pasade.

Being fully aware of how frequently spontaneous remissions occur in diabetic retinopathy, I am making no claims for the therapeutic value of PAS in this condition. My experience in a short follow-up of these and other cases, however, appears to justify further evaluation.

Trials with Deca-durabolin, vitamin B₁₂, Lipotriad, and Venoruton P 4, have not convinced me that these drugs are of therapeutic value. There is very little justification for keeping patients on a type of treatment which is going to increase the hardship of living with diabetes unless it is likely to be of some benefit. The same comment might be made regarding an unduly austere diet, with animal fats replaced by corn oil or a suitable variety of margarine.

Thus the answer to my friend's question what can we do for our patients with diabetic retinopathy is as follows: When patients with retinopathy come to us for advice it is not right that we should adopt evasive action and refer them to their medical adviser, although any advice we give should be the result of joint consultation. A maximum effort should be made in the early stages to prevent the onset of retinopathy and to arrest its progress if present. In the regrettable absence of any effective therapy, the onset of diabetes should be anticipated by the institution of detection drives and screening tests, organized at the national level. Should diabetes become overt it must be rigidly controlled in the early years, preference being given to two injections of soluble (rather than to the long-acting) insulins, with a view to achieving better 24-hour control. The diet should be properly balanced, with reduction of animal fats or their replacement by vegetable oils, care being taken not to convert juveniles into psychological invalids by unreasonable austerity. The use of any form of therapy which has proved to be of benefit in other cases would be justified, even if only to keep up the patient's

morale, to give them the feeling that interest is being taken in their ocular welfare—in short, that some effort is being made on their behalf.

Major contributions in the realm of diabetic research have been made by pathologists, biochemists, endocrinologists, neurosurgeons, metabolic specialists, and others. Since Ballantyne's Doyne Lecture in 1946, outstanding works in the field of clinical ophthalmology have been infrequent, although Alerts and Slosse, Lundbaek, and Babel and Rilliet have recently published their experiences and views. The field of diabetic retinopathy was covered from every aspect of at the Haddonfield Conference in 1960 and to my knowledge no advance in prophylaxis or therapy has taken place since then. I feel that ophthalmologists should concentrate more on this manifestation in the reasonable assumption that it will be the commonest cause of blindness in the years to come and with the conviction that its cause will be discovered in the foreseeable future. It is my view that a closer liaison between ophthalmologists and other workers in this field is the policy most likely to pay dividends. None of us can be conversant with all the various approaches to this problem but, by careful study of individual cases in co-operation with other specialists and the pooling of knowledge, we may fill the remaining gaps in what one might compare with a jig-saw puzzle.

Four names are internationally known for their pioneering work in diabetes mellitus: Banting, Best, Joslin, and Lawrence. To these, and many others, are due the thanks of diabetics and the parents of diabetics. The death sentence of the pre-insulin era has been commuted to a life sentence of comparatively normal existence, but there is a threat of long-term vascular complications.

Addressing diabetics in 1960, Charles Best said:

"Laboratories the world over are working on your problems. The advances in the future will bring you at least as much benefit as have those of the past 40 years."

In the confidence that this forecast is correct we hope that the first of these advances will be the discovery of the cause and prevention of diabetic retinopathy—the challenge that you have accepted here to-day.

(This address was illustrated by means of numerous fundus transparencies, many of which were projected simultaneously in order to demonstrate the appearance of the retinopathy before and after treatment.)