

DIABETIC RETINOPATHY DEVELOPING IN TWO CASES ON TOLBUTAMIDE THERAPY

T. SCHNEIDER, M.D. (RAND), F.R.C.P. (EDIN.) and L. MEYERSON, M.B., B.Ch., D.O. R.C.P. & S.

Diabetic Clinic, Johannesburg General Hospital, Johannesburg

A great deal of interest has been stimulated in the treatment of diabetes mellitus as the result of the introduction of the sulphonyl ureas during the past 3 years. One of these substances (tolbutamide, D 860), has proved effective^{1, 2} in over 40% of the middle-old-age group. The patients who have responded to treatment have been kept under good control so far as blood sugar and urine estimations have shown. They have remained symptom-free and have felt well. However, the great challenge in treatment of diabetes still remains that of the occurrence of the late manifestations of the disease. Vascular changes, hypertension, albuminuria, retinopathy, possibly cataract, and Dupuytren's contraction have all been described in this category.

Even where good control of diabetes has been maintained with insulin therapy, the late manifestations have ultimately appeared. It was hoped that with tolbutamide therapy this would not occur. While realizing that a long period of time must elapse before it will be possible to evaluate the true effects of tolbutamide therapy, we feel that it is important to report any late manifestations occurring during the course of treatment.

One of us (L.M.) has made repeated ophthalmological examinations of tolbutamide-treated patients at the Diabetic Clinic, particular attention being paid to the development of retinopathies or other ocular changes occurring during the course of therapy. As a result it is now possible to record 2 cases in which retinopathies have occurred during treatment.

CASE 1

Mrs. I.J.C.M., aged 61 years, presented with diplopia to the right due to a right external rectus palsy. On investigation she was found to be diabetic, with a heavy glycosuria and a fasting blood sugar of 257 mg. per 100 ml. On diet plus 15 U. of lente insulin the patient became asymptomatic and the rectus palsy disappeared. Her fasting blood sugar, however, still remained

TABLE I

| Date | Blood Sugar | Fundi |
|-----------|-------------|---|
| *28/ 6/56 | 257 | Normal. |
| *27/ 7/56 | 245 | |
| *27/ 9/56 | 245 | |
| 27/11/56 | 126 | |
| 11/12/56 | 121 | |
| 9/ 1/57 | 131 | |
| 7/ 2/57 | 115 | |
| 26/ 2/57 | 91 | |
| 29/ 3/57 | 81 | |
| 3/ 5/57 | 112 | |
| 24/ 6/57 | 134 | Many micro-aneurysms and punctate haemorrhages, occasional blotch haemorrhages. |
| 5/ 7/57 | 122 | |
| 2/ 8/57 | 87 | |
| 30/ 8/57 | 103 | |
| 27/ 9/57 | 110 | |
| 8/10/57 | 135 | |
| 19/11/57 | 95 | |
| 10/12/57 | 104 | |
| 10/ 1/58 | 95 | |
| 31/ 1/58 | 103 | |
| 7/ 3/58 | 105 | |
| 1/ 4/58 | 116 | |
| 2/ 5/58 | 101 | Micro-aneurysms, punctate and blotch haemorrhages, discrete exudates. |
| 14/ 5/58 | 100 | |
| 21/ 5/58 | 77* | |
| 28/ 5/58 | 83* | |
| 30/ 5/58 | 102 | |
| 27/ 6/58 | 119 | |

Blood sugar expressed in mg. per 100 ml. blood. All samples taken fasting except those marked *, which were random samples taken 3 hours after a meal.

high, being 245 mg. per 100 ml. both in July and September 1956. The fundi remained normal throughout.

In October 1956 she was transferred to tolbutamide therapy. Her blood sugar responded immediately and has remained at near normal limits since that time (Table I). In spite of the marked improvement in the diabetic state and the fact that she was perfectly well, gradual changes occurred in the eye grounds from January 1958 onwards. At first only a few micro-aneurysms and occasional punctate and blotch haemorrhages made their appearance but within a matter of a few months the condition had worsened considerably until it was that of an advanced retinopathy with micro-aneurysms, punctate and blotch haemorrhages and discrete exudates throughout both fundi. In June 1958 a slight improvement in the retinopathy was noted, but the condition still remain very marked.

CASE 2

Mrs. F.E., aged 68 years. Diabetes mellitus was discovered in June 1957, her first symptoms being mistiness of vision, thirst and loss of weight. Early lenticular changes were present in both eyes; although arteriosclerotic changes were seen there was no evidence of diabetic retinopathy. A further independent ophthalmic opinion 3 months later confirmed the first findings.

Tolbutamide therapy was commenced on 13 June 1957. It will be seen in Table II that although the blood sugar was high

TABLE II

| Date | Blood Sugar | Fundi |
|----------|-------------|--|
| 13/ 6/57 | 368 | Early lenticular changes. Fundi normal except for arteriosclerosis. |
| 2/ 7/57 | 204 | |
| 9/ 7/57 | 161 | |
| 6/ 8/57 | 308 | |
| 15/ 8/57 | 195 | |
| 5/ 9/57 | 167 | |
| 3/10/57 | 151 | |
| 29/10/57 | 168 | |
| 26/11/57 | 120 | |
| 24/12/57 | 125 | |
| 17/ 1/58 | 139 | Many micro-aneurysms and punctate haemorrhages plus occasional blotch haemorrhage. |
| 18/ 2/58 | 129 | |
| 17/ 5/58 | 140 | |
| 20/ 6/58 | 112 | |

All samples taken fasting.

originally there has been a gradual drop to near normal limits. Control has not been so good as in Case 1, but the blood sugars have been returning to near normal levels and this patient is under effective diabetic control. In spite of her improved condition and the disappearance of all symptoms, retinal changes have appeared.

The first signs of the changes were noted in January 1958, when micro-aneurysms and punctate and blotch haemorrhages were discovered. These have remained constantly present during the past few months.

DISCUSSION

Two diabetic cases are described who have developed retinopathy while under effective control on tolbutamide therapy. In the one case diabetes has been present for a period of 2 years and in the other for a period of 7 months. In case 1 control of the diabetes has been very good on a regime of tolbutamide plus diet. In spite of this, retinopathy has appeared and advanced rapidly. In case 2 the control has not been as good as in the former, but there has been no glycosuria and the blood sugar has not been markedly raised.

Retinopathy is one of the very distressing late mani-

festations of the disease. While no claims have been made that tolbutamide would prevent the onset of this condition or other late manifestations of diabetes, it was hoped that effective control with this remedy might have this result. The 2 cases described, however, suggest that this is not the case.

The high incidence of retinopathy in diabetes is well known. The longer the duration of diabetes the higher would appear to be the incidence. Waite and Beetham⁴ state that 59% of their patients with diabetes of 15 years' standing or more have retinopathy, and Wagener⁵ that 60% of more than 10 years standing show a similar condition. Whittington and Lawrence⁶ state that 75% with diabetes of 20 years' standing or more show retinal changes, and Ballantyne⁷ found 31.7% of cases with retinopathy among 561 diabetics of all ages. Wagener⁸ gives a figure of 30.6 for diabetic retinopathy among patients of all ages. One of us (T.S.)⁹ found 58 cases of retinopathy among 231 diabetics, 14 of whom showed the condition 0.5 years after the diabetes had commenced.

It is evident that retinopathy may occur early in the course of diabetes, and Wagener⁵ has pointed out that in occasional cases of retinopathy the only evidence of diabetes is a positive glucose-tolerance curve. He has suggested that 'a primary disturbance of carbohydrate metabolism is requisite to the institution of the retinopathy, but that this disturbance need not be sufficiently severe to cause permanent elevation of the blood-sugar levels, and that some secondary defect of metabolism may be the actual cause of the retinopathy'.

On the other hand, Fisher⁹ states that the principal factor responsible for the development of diabetic retinopathy is long-standing hyperglycaemia, and the best method available at present for the prevention of the degenerative complications of diabetes is exact control of the diabetes through training of the diabetics themselves. Dunlop¹⁰ maintained 39 diabetics on a 'free diet' for 9 years and degenerative complications, including retinopathy, developed in 14 (36%). In a group of 15-31 years duration he found retinopathy in 44% of those with good control and in 79% of those with poor control. He has decided that careful control and aggressive treatment of the diabetes over the years are most important factors in the prevention or postponement of diabetic degenerative lesions.

It is therefore controversial whether good control of diabetes is the answer to the problem of the prevention of retinopathy and the other diabetic degenerative lesions.

Close similarity has been found between the lesions in

diabetic retinopathy and those in the Kimmelstiel-Wilson syndrome. Further, both the retinopathy and the renal lesions have been produced in alloxan-diabetic animals by injecting corticotrophin.¹¹ It has been observed in our clinic that patients experiencing emotional upsets (e.g. the loss of a husband) have had a marked exacerbation of their retinopathy, which may be due to an outpouring of cortisone during a stress period. Thus the possibility that a hormonal disturbance may be a factor in the causation of the retinopathy cannot be discounted.

It would therefore appear that something more than the effective control of diabetes will be necessary before the elimination of the late manifestations of diabetes becomes possible. Whilst patients are symptomatically better under good control they continue to be dogged by the spectre of the late manifestations.

Good control was maintained with tolbutamide in 42.9% of cases in a middle- to old-aged group at our clinic, and a further 28.3% were kept under fair control.² The drug has now been used at the clinic for almost 2 years without any serious toxic effects and it can therefore be considered a valuable addition to our armamentarium in the fight against diabetes mellitus. However, the appearance of cases of retinopathy in the effectively treated group suggests that it will be necessary to continue looking for factors others than hyperglycaemia in its causation and possibly in the occurrence of other late manifestations.

SUMMARY

1. Two cases of diabetes mellitus are described who have developed retinopathy while on tolbutamide therapy.
2. In one case diabetic control was good and in the other it was fair.
3. The question of the occurrence of retinopathy in relationship to the control of diabetes is discussed.
4. The suggestion is made that some other factor besides hyperglycaemia may be the cause of diabetic retinopathy and possibly other late manifestations of diabetes.

REFERENCES

1. Schneider, T. and Politzer, W. M. (1957): *S. Afr. Med. J.*, 31, 142.
2. Schneider, T., Lopis, S. and Politzer, W. M. (1958): *Ibid.*, 32, 149.
3. Schneider, T. (1953): *Ibid.*, 27, 466.
4. Waite, J. H. and Beetham, W. P. (1935): *New Engl. J. Med.*, 212, 367 and 429.
5. Wagener, H. P. (1946): *J. Omaha Clin. Soc.*, 7, 43.
6. Whittington, T. H. and Lawrence, R. D. In Soresby, A. ed. (1951): *Systemic Ophthalmology*, p. 334. London: Butterworth.
7. Ballantyne, A. J. (1946): *Trans. Ophthal. Soc. U.K.*, 66, 503.
8. Wagener, H. P. (1945): *Proc. Mayo Clin.*, 37, 414.
9. Fischer, F. (1954): *Klin. Mbl. Augenheilk.*, 125, 666.
10. Dunlop, D. M. (1954): *Brit. Med. J.*, 2, 383.
11. Becker, B. (1952): *Ann Intern. Med.*, 37, 273.