Recent advances in the treatment of diabetic retinopathy

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Contributed by request and dedicated to Sir Stewart Duke-Elder

The lesions which may be present in diabetic retinopathy are diverse, and the research, both clinical and histopathological, which has been necessary to elucidate their formation and evolution, has had to be laborious and prolonged. These studies have, however, led to the use of some well-defined therapeutic measures which are undoubtedly of value in this condition which is now the leading cause of blindness in patients under 65 years of age in Great Britain (Sorsby, 1973).

A patient with diabetic retinopathy may lose vision in one of two conditions which often co-exist:

(1) Because of bleeding from new vessel formations or later from vitreous opacities and secondary traction effects on the retina (Proliferative diabetic retinopathy).

or

(2) Retinal oedema, deposition of lipid, pre-retinal fibrosis, or capillary closure in the macular area (Simple or exudative diabetic retinopathy or, better, diabetic maculopathy).

As in most medical conditions, treatment is most effective in the early stages; that is to the new vessel formations in proliferative retinopathy and to oedema due to foci of capillary damage in diabetic maculopathy. At the present time many patients are referred when secondary changes, such as connective tissue bands, large lipid deposits, and pre-retinal fibrosis are well established; in these later stages attempts at treatment are largely unrewarding.

Treatment of proliferative diabetic retinopathy

Repeated vitreous haemorrhages occur mostly in cases of diabetes of juvenile onset or in diabetic patients under 50 years of age, but they are even more serious when occurring in older patients (Patz and Berkow, 1968). There is danger of rapid and permanent loss of sight due to bleeding from the new vessels characteristic of the condition. The new vessels occur on the disc in some 73 per cent. of cases and frequently at the site of the arterio-venous crossings of the main retinal vessels (Taylor and Dobree, 1970). There are four major avenues of approach in therapy; photocoagulation, pituitary ablation, general measures, and surgery.

(i) Photocoagulation

This was first advocated by Wetzig and Worlton (1963) using a xenon arc photocoagulator. The rationale of the treatment is to eradicate as many of the new vessel formations as

early a stage as possible and thus to prevent bleeding and the later cicatricial effects. New vessels lying flat on the plane of the retina are the most obvious target of attack but even "forward" vessels attached to the retracted vitreous face (Davis, 1965) can be coagulated (Okun and Cibis, 1966). The site of bleeding which has caused a pre-retinal haemorrhage can often be identified from small residual haemorrhages lying adjacent to the bleeding new vessels or to a trail of small clots leading from them to the pooled blood. A small bleeding episode, often unnoticed by the patient, may herald a large one and a most insignificant group of new vessels may be responsible for a disastrous haemorrhage.

Disc vessels are a formidable problem to local photocoagulation although several workers have advocated treatment to vessels lying at the nasal edge of the disc or with caution actually on the disc itself (Wetzig and Jepson 1969). The argon laser developed by L'Esperance (1969) has been used in this situation to obliterate feeder arterioles in new vessel formations on the disc (Patz, 1972; Zweng, Little, and Peabody, 1969, 1971a,b; Behrendt, 1972), but the method is often complicated by haemorrhage (Goldberg and Herbst, 1973). Another method is to "reduce the vascular activity" of the whole retina by partial ablation by multiple retinal coagulations. This was first advocated by Aiello, Beetham, Balodimos, Chazan, and Bradley (1969) using multiple widely scattered laser burns, but more recent trends have been towards ablating the periphery of the retina; Taylor (1970) has calculated that it is necessary to ablate an area of retina of at least one seventh of the total area to obtain a regression of disc vessels. Unfortunately regression takes place in only a limited number of cases but the tendency to bleed may be reduced in others.

To be effective, photocoagulation must be done in the earlier stages of the condition, for it is then that bleeding is more liable to occur. The natural course of proliferative retinopathy is towards cicatrization and light coagulation is unlikely to help cases in which there is dense connective tissue formation around new vessels, and may cause retinal detachment if used on vascularized bands on the surface of the retina. Furthermore, the presence of fibrosed arterioles (white line appearance) indicates retinal ischaemia in the area supplied by the arteriole, and "new vessels" in these areas are often dilatations of pre-existing capillary channels and appear to be compensatory in nature.

Because of the wide variations in the severity of proliferative retinopathy in the two eyes and the fluctuations in the visual acuity during the bleeding episodes, there are still no figures by which the results in treated and untreated eyes from the same individual can be compared. It must be stated, however, that, where actual and potential bleeding sites can be identified and effectively coagulated, the prognosis is considerably improved in any individual eye. Furthermore, photocoagulation has an established value in other conditions in which sub-hyaloid and vitreous bleeding occurs from new vessel formations such as in Eales's disease, sickle cell disease (Goldberg, 1971), and new vessels following arteriosclerotic branch vein thrombosis (Krill, Archer, and Newell, 1971).

(ii) *Pituitary ablation*

Even in the most experienced hands there is a disturbing morbidity and mortality accompanying this procedure which undoubtedly causes an improvement in the vascular new formations of proliferative retinopathy, and this is particularly marked in the cases of florid retinopathy, sometimes called rubeosis of the retina, a fortunately rare condition found in juvenile diabetics in which almost the whole retina is covered by rapidly extending new vessel formations. An ablation combined with light coagulation to particularly active areas seems to afford the best prognosis in these otherwise hopeless cases (Beaumont and Hollows, 1972; Kohner, Joplin, Blach, Cheng, and Fraser, 1972).

(iii) Control of diabetes and general measures

Kohner, Fraser, Joplin, and Oakley (1969) have produced evidence that the onset of diabetic retinopathy is delayed and its severity mitigated in those patients with excellent, as opposed to poor, control of their diabetes. It may also be possible and it is certainly not proven that diabetics with a high blood sugar are more liable to bleeding episodes than when the blood sugar is low. Few surgeons, it should be noted, would operate on a diabetic cataract if the blood sugar was known to be raised. Treatment of any accompanying hypertension or haemopoietic disease is also mandatory.

The avoidance of any condition, mechanical or medical, which increases the venous pressure in the head and neck must almost certainly have a beneficial effect in reducing the likelihood of intraocular haemorrhage. If normal retinal vessels can break during a Valsalva manoeuvre (Duane, 1973) it is likely that lifting, particularly in a squatting position, sneezing, coughing, vomiting, and straining at stool, put pathological vessels in grave peril of rupture. Rest in bed is a valuable measure in speeding up the absorption of vitreous haemorrhages (Dobree and Taylor, 1973).

(iv) Surgery

The late cicatricial stages of proliferative retinopathy, their traction effects, and their relation to retinal detachment, have been very fully described by McMeel (1971). Okun and Fung (1969), McMeel (1971), Tasman (1972), and others have successfully tackled these most difficult surgical problems. The basic principle behind the procedures is to reduce tension on the bands causing actual or potential detachment or schisis by scleral indentation or shortening in the appropriate sectors.

Vitrectomy is still in its infancy and has been used with success in cases of dense vitreous haemorrhages which have failed to absorb and for the removal of opaque vitreous membranes (Machemer and Norton, 1972).

Treatment of diabetic maculopathy

Focal areas of capillary closure in the posterior pole are associated with pathological capillaries (Levene, Horton, and Gorn 1966; Kohner and Dollery, 1970), which are revealed ophthalmoscopically as collections of small red dots which Ashton (1949) has shown to consist of microaneurysms, varicose capillaries, and small round haemorrhages. These presumably hypoxic areas are particularly numerous immediately lateral to the macula and above and below it, and may leak profusely as shown by fluorescein angiograms. Later lipid deposits are formed as rings either around the leaking oedematous areas or as larger plaques deposited particularly in the macular region where their presence may lead to visual loss (Dobree, 1970). It is not surprising that early attempts to restore vision by altering the blood biochemistry by a low fat intake and replacement of animal fats by unsaturated fats (King, Dobree, Kok, Foulds, and Dangerfield, 1963) or by clofibrate (Cullen, Ireland, and Oliver, 1964) failed to achieve this object, although a marked absorption of the lipid deposits in the retina was produced by both methods.

More recently direct photocoagulation has been applied to the areas of leaking capillaries and a statistically significant visual improvement has been shown (Hill, 1972) as the pathological areas have been converted to fibrotic scars. This technique was first used by Meyer-Schwickerath (1959) who reported five cases. Wessing and Meyer-Schwickerath (1969) reported further results at the Airlie House Symposium, and at the same Symposium Welch (1969) reported dramatic improvement in vision after treatment in cases in which

the macula was involved in a circinate lipid deposit. Photocoagulation of the capillary lesions at the centre of these rings caused rapid clearing of the retinal oedema and surrounding lipid. Spalter (1971a, b) reported the favourable effects of photocoagulation in cases of simple diabetic retinopathy using a Xenon arc photocoagulator, and this was confirmed by Rubinstein and Myska (1971, 1972). Patz, Maumenee, and Ryan (1971) obtained similar results using the argon laser. The selection of patients who are likely to benefit from either type of photocoagulation requires both clinical judgement and the help of fluorescein angiography. It is of great significance when there is a recent drop of one or two lines in the visual acuity of an eye with macular changes, particularly if there is photographic evidence that lipid is being pooled in the macular area. If macular deposits form part of a ring of exudate, it is sometimes possible to photocoagulate the central lesion on the evidence of serial fundus photographs alone. Fluorescein studies provide much additional information. Paramacular leaking areas which may be localized or diffuse appear from the time of the early venous phase of the transit, and it must be remembered that leakage from a site of up to $1\frac{1}{2}$ disc diameters from the macula may cause oedema and deposition of lipid there. Angiograms also show the presence of islets of capillary closure ("non-perfusing capillaries") in the para-macular area or macular cystoid changes, the presence of either condition adversely affecting the prognosis of treatment (Ticho and Patz, 1973). Good results can be expected if the burns are small and multiple, and the macroscopic macular vessels can be avoided. It often takes 3 to 6 months before visual improvement occurs.

The outlook in a case of diabetic retinopathy is considerably better than it was a decade ago; this is not so much because of an increased efficiency of the therapeutic weapons, but because of a better knowledge of the natural evolution of the condition and an awareness of the need to treat diabetic lesions in the early, rather than the late, stages. Regular surveillance of all diabetics and in particular those with established retinopathy is therefore of paramount importance.

References

- AIELLO, L. M., BEETHAM, W. P., BALODIMOS, M. C., CHAZAN, B. I., and BRADLEY, R. F. (1969) In "Symposium on the Treatment of Diabetic Retinopathy, 1968", ed. M. F. Goldberg and S. L. Fine, ch. 35, p. 437. U.S. Public Health Service Publication No. 1890. Washington, D.C.
- ASHTON, N. (1949) *Brit. J. Ophthalm.*, **33**, 407
- BEAUMONT, P., and HOLLOWS, F. C. (1972) *Lancet*, **1**, 419
- BEHRENDT, T. (1972) *Arch. Ophthalm. (Chicago)*, **87**, 629
- CULLEN, J. F., IRELAND, J. T., and OLIVER, M. F. (1964) *Trans. ophthalm. Soc. U.K.*, **84**, 281
- DAVIS, M. D. (1965) *Arch. Ophthalm. (Chicago)*, **74**, 741
- DOBREE, J. H. (1970) *Brit. J. Ophthalm.*, **54**, 1
- and TAYLOR, E. (1973) *Ibid.*, **57**, 73
- DUANE, T. D. (1973) *Amer. J. Ophthalm.*, **75**, 637
- GOLDBERG, M. F. (1971) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **75**, 532
- and HERBST, R. W. (1973) *Arch. Ophthalm. (Chicago)*, **89**, 311
- HILL, D. W. (1972) *Trans. ophthalm. Soc. U.K.*, **92**, 125
- KING, R. C., DOBREE, J. H., KOK, D'A., FOULDS, W. S., and DANGERFIELD, W. G. (1963) *Brit. J. Ophthalm.*, **47**, 666
- KOHNER, E. M., and DOLLERY, C. T. (1970) *Brit. med. Bull.*, **26**, 166
- , FRASER, R. T., JOPLIN, G. F., and OAKLEY, N. W. (1969) "The effect of diabetic control on diabetic retinopathy", in "Symposium on the Treatment of Diabetic Retinopathy, 1968", ed.

- M. F. Goldberg, and S. L. Fine, p. 119. U.S. Public Health Service Publication No. 1890. Washington, D.C.
- , JOPLIN, G. F., BLACH, R. K., CHENG, H., and FRASER, R. T. (1972) *Trans. ophthalm. Soc. U.K.*, **92**, 79
- KRILL, A. E., ARCHER, D., and NEWELL, F. W. (1971) *Arch. Ophthalm. (Chicago)*, **85**, 48
- L'ESPERANCE, F. (1969) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **73**, 1077
- LEVENE, R., HORTON, G., and GORN, R. (1966) *Amer. J. Ophthalm.*, **61**, 283
- MACHEMER, R., and NORTON, E. W. D. (1972) *Ibid.*, **74**, 1034
- MCMEEL, J. W. (1971) *Trans. Amer. ophthalm. Soc.*, **69**, 440
- MEYER-SCHWICKERATH, G. (1959) Bücherei des Augenarztes No. 33
- OKUN, E., and CIBIS, P. A. (1966) *Arch. Ophthalm. (Chicago)*, **75**, 337
- and FUNG, W. E. (1969) "Therapy of diabetic retinal detachment", in "Symposium on Retina and Retinal Surgery", Trans. New Orleans Academy Ophthalm., ch. 21, p. 319. Mosby, St. Louis
- PATZ, A. (1972) "Argon laser photocoagulation in diabetic retinopathy", in "Causes and Prevention of Blindness", ed. I. C. Michaelson and E. R. Berman, p. 319. Academic Press, New York/London
- and BERKOW, J. W. (1968) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **72**, 253
- , MAUMENEE, A. B., and RYAN, S. J. (1971) *Ibid.*, **75**, 569
- RUBINSTEIN, K., and MYSKA, V. (1971) *Trans. ophthalm. Soc. U.K.*, **91**, 355
- and ——— (1972) *Brit. J. Ophthalm.*, **56**, 1
- SORSBY, A. (1973) *Hlth Trends*, **5**, 7
- SPALTER, H. F. (1971a) "Photocoagulation of macular lesions in diabetic retinopathy", in "Ophthalmology: Proc. XXI Int. Congr. Ophthalm. Mexico, 1970", p. 885. Excerpta Medica, Amsterdam
- (1971b) *Amer. J. Ophthalm.*, **71**, 242
- TASMAN, W. (1972) *Arch. Ophthalm. (Chicago)*, **87**, 286
- TAYLOR, E. (1970) *Brit. J. Ophthalm.*, **54**, 535
- and DOBREE, J. H. (1970) *Ibid.*, **54**, 11
- TICHO, U., and PATZ, A., (1973) *Amer. J. Ophthalm.*, **76**, 880
- WELCH, R. B. (1969) In "Symposium on the Treatment of Diabetic Retinopathy, 1968", ed. M. F. Goldberg and S. L. Fine, ch. 47, p. 563. U.S. Public Health Service Publication No. 1890. Washington, D.C.
- WESSING, A. K., and MEYER-SCHWICKERATH, G. (1969) *Idem*, p. 569
- WETZIG, P. C., and JEPSON, C. N. (1969) *Idem*, p. 593
- and WORLTON, J. T. (1963) *Brit. J. Ophthalm.*, **47**, 539
- ZWENG, H. C., LITTLE, H. L., and PEABODY, R. R. (1969) "Laser Photocoagulation and Retinal Angiography". Mosby, St. Louis
- , ———, ——— (1971a) "Further Observations of Argon Laser Photocoagulation of Diabetic Retinopathy". Amer. Academy of Ophthalm. Otolaryng., Las Vegas
- , ———, ——— (1971b) *Arch. Ophthalm. (Chicago)*, **86**, 395