Communications

Pathogenesis and treatment of diabetic maculopathy

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Our preliminary report on the treatment of diabetic maculopathy concerned 44 eyes in forty consecutive patients treated during the 2 years prior to January, 1971 (Rubinstein and Myska, 1972). During the following 2 years (until January, 1973) yet another 77 eyes (in 72 patients) have been treated in a similar manner, bringing our clinical material to 121 eyes in 112 patients with a follow-up of between a maximum of 4 years and a minimum of 2 years for the previously reported group, and between 2 years and 6 months for the second. It is felt that such a number of clinical cases and the follow-up running into 4 years justify a re-assessment of the efficiency of this treatment and the validity of the principles on which it is based.

Working hypothesis

As a result of diabetic microangiopathy multiple foci of tissue hypoxia develop in the retina. An hypoxic focus of partially collapsed and abnormally permeable capillaries is flanked by abnormal blood shunting channels of variably thickened walls and variably uneven calibre, developing microaneurysms and unable to maintain the physiological blood–retina barrier. The result of these changes is an area of acidosis and tissue oedema spreading centrifugally and self-perpetuating. The abnormal vessel permeability to plasma causes—in the first instance—tissue oedema and, if increased, haemorrhages by red corpuscle diapedesis. Permeability to plasma lipids manifests itself as deposits of hard exudates, and new vessel formation results from stimuli not yet fully understood but likely to include hypoxia and lactic acid accumulation. The hypoxic focus of diabetic retinopathy seems to be the basic anatomical lesion and it carries a pathogenic potential (Fig. 1, opposite).

There are four ways in which a macula may be affected by the presence of an hypoxic focus in its vicinity (being avascular the macula itself does not become the centre of a primary hypoxic focus):

(a) By an advancing front of oedema;
(b) By advancing new vessels;
(c) By a haemorrhage;
(d) By deposition of hard exudates.
Pathogenesis and treatment of diabetic maculopathy

The first sign of diabetic maculopathy is macular oedema. This is often compatible with a long period of retention of good central vision, but eventually sensory and pigment epithelial degeneration will take place with failing visual acuity. Any therapeutic interference to be effective would have to be early, before permanent anatomical damage to the macula had time to develop.

The primary aim of our treatment is to convert the hypoxic foci, which are threatening the macula by their advancing front, into anoxic foci—scars—which carry no such pathogenic potential (Rubinstein and Myska, 1971). Closure of the diseased capillaries and new vessels at the centre of a focus lead to the absorption of oedema, hard exudates, and haemorrhages, and the closure of microaneurysms. In early cases with only one or two foci around the macula, a few photocoagulation burns suffice (direct approach) (Fig. 2). A common remote hypoxic area is the temporal raphe which can be effectively and safely photocoagulated. This area often shows more extensive changes requiring six to twelve applications (paramacular approach) (Fig. 3). In florid cases, where the whole perimacular area is studded with hypoxic foci which merge and lose their identity, such precise targeting may be impossible, and destruction of as many foci as practicable without depriving the macular retina of all circulation is performed by the use of perimacular multiple application along the arcuate perimacular vessels. About twenty to thirty applications are then required (perimacular approach) (Fig. 4). In cases of massive or widespread changes in all the posterior pole area accompanied by similar or proliferative changes in the rest of the fundus, a peripheral pattern bombarding technique is added, the number of applications some-
FIG. 2 Fluorescein angiograms
(a) Three hypoxic foci with circinate rings. The hard exudates of the large middle focus are situated at the macula
(b) After three light coagulation burns, each applied to a centre of the focus

FIG. 3 Paramacular approach (to the temporal raphe). F—macula. Fluorescein angiogram
FIG. 4 Perimacular approach. Fluorescein angiogram

times reaching 200 (peripheral pattern bombing) (Fig. 5). The assessment of the retina and the choice of approach must be based on fluorescein angiography. This alone is capable of defining areas of circulatory disturbance requiring treatment as opposed to inactive exudates, haemorrhages, and microaneurysms which do not require direct destruction (Rubinstein, 1969; Rubinstein and Myska, 1970).

Clinical material
Of more than 300 diabetics treated by light coagulation for retinopathy during the years 1968 to 1972, 112 were treated specifically for macular changes; in nine patients both eyes were treated. The
Pathogenesis and treatment of diabetic maculopathy

FIG. 5 Scheme of the five methods of treatment. Numbering as in Table I

The trial was planned on the principle of leaving the better eye untreated as a control. The nine patients who eventually had the second eye treated also, showed, during the period of observation, such a deterioration of the visual acuity of the untreated eye—as contrasted with improvement or arrest of retinopathy in the treated eye—that at some stage their inclusion in the programmed trial had to be abandoned on ethical grounds. The 112 patients included 65 males and 47 females, and the age distribution was as follows: 28 to 40 years, eight; 41 to 50 years, fourteen; 51 to 60 years, 44; over 61 years, 46.

The preoperative visual acuity of the treated eyes (Table I) shows a wide range of macular dysfunction, the mean visual acuity of the series falling just above 6/18.

Table I Preoperative visual acuity (in 121 treated eyes)

<table>
<thead>
<tr>
<th>Method</th>
<th>Visual acuity</th>
<th>Less than</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Centres of circinate rings</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(2) Leaking and new vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Perimacular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(4) Paramacular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5) Peripheral pattern bombing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>
Selection and management of patients

The routine management of the patients—after earlier experimentation—was established as follows:

Referred patients were seen by appointment and a decision was made as to their suitability for treatment. Those selected, and all doubtful cases, had fundus photography done and angiography of relevant retinal sectors—using 4 ml. 10 per cent. fluorescein sodium intravenously—at that first visit. After the photographs and angiograms had been studied, a final decision was made about the feasibility and method of treatment.

The indication for treatment was the presence of subjective visual symptoms relating to macular involvement, however early (e.g. some distortion of vision even with visual acuity 6/5) or however late (e.g. visual acuity of 1/60), and the presence of macular pathology, however negligible (e.g. early oedema) or however advanced (pigment dystrophy, large hard deposits, heavy haemorrhagic involvement of all the central area).

The contraindications for treatment were:

(a) A degree of lens sclerosis high enough to prevent clear observation and the production of an efficient retinal burn;
(b) Pre-retinal membranes over areas requiring direct treatment;
(c) Marked gliosis at and round the essential target areas.

All but ten operations were conducted on a day-patient basis. The exceptions were those patients who insisted on general anaesthesia, who were judged to require general anaesthesia because of obvious psychological instability, or who could not reach the hospital from home on the morning of the operation because of the distance involved. We do not consider it prudent—unless necessary—to admit diabetics into an eye unit.

All but four operations were done under local anaesthesia. Premedication with Droperidol 5 mg. and Phenoperidine 0.5 mg. 1 hour before operation was followed in the light coagulation theatre with slow intravenous infusion of Valium (3 to 5 mg.) and retrobulbar injection of Lignocaine 3 ml. These measures assured relaxation of the patients, often to the point of snoring, and an immobile eye often requiring no lid speculum and no fixation forceps for positioning. Occasional sliding of the upper lid over the cornea by the operator’s finger maintains a moist and clear cornea. Most patients had none or only a vague memory of the procedure even in cases of maximum targeting. After light coagulation they were rested recumbent for 2 to 3 hours and then allowed to go home. The first postoperative checks were done within 7 days after treatment.

Instrumentation

Xenon light generated by the Zeiss (Oberkochen) instrument was used in the first part of this trial and that of the Log-2 O’Malley Coagulator in the second. Of the two the latter proved to be a much easier instrument to use and of equal efficiency. Particularly for the work near the macula, the O’Malley aperture 2° with appropriate power setting was much safer and more efficient than the Zeiss aperture 1.5, mainly because of better visibility of the surrounding field, facilitating targeting. The time of a single application was never more than 2 sec., mostly less, and we aimed at definite lesions but of minimal strength. Table II shows the frequency of each of these approaches.

**Table II  Methods of treatment and number of eyes**

<table>
<thead>
<tr>
<th>Method</th>
<th>I Direct</th>
<th>(1) Centres of rings</th>
<th>54</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2) New vessels</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>II Indirect</td>
<td>(3) Perimacular</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>(4) Paramacular</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>(5) Peripheral pattern bombing</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Total eyes 121
Complications

From fluorescein angiography We had no case of anaphylactic reaction to fluorescein in this series.

From premedication In three cases we had difficulties with sedation by our measures; the patients had to have treatment under general anaesthesia later on. We had no case of untoward reaction from our sedation.

From retrobulbar injections None. We had one case of temporary acute occlusion of the central retinal artery and a lightning rise in intraocular pressure after retrobulbar injection, before the beginning of this trial. The injection was one of Lignocaine with adrenaline; the recovery was full within 1 hour but we banned adrenaline from further work.

From light coagulation The following complications from light coagulation could be anticipated: haemorrhages, vitreous shrinkage, macular puckering, macular damage. We encountered none of these. Regarding visual field changes, apart from one case in the early series, no sector scotomata were produced. Localized small scotomata reciprocal with light coagulation scars can be demonstrated in most cases but they are not subjectively appreciated.

Results

Of the 121 treated eyes, improvement of visual acuity was achieved in 65 (31 by 1 line, 24 by 2 lines, nine by 3 lines, one by 5 lines—Snellen chart). Maintenance of preoperative visual acuity was obtained in 47 eyes. In this group nine eyes had a preoperative visual acuity of 6/6 or better. Deterioration of visual acuity occurred in nine eyes; of these four had preoperative lens opacities which were progressive and they account for all three cases of deterioration in excess of 1 line (Table III).

Table III Visual acuity change in 121 treated eyes (follow-up 6 mths to 4 yrs)

<table>
<thead>
<tr>
<th>Visual acuity</th>
<th>Improved</th>
<th>Same*</th>
<th>Worse**</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lines (Snellen chart)</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Centres of circinate rings</td>
<td>1</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Leaking and new vessels</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Perimacular</td>
<td>1</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Paramacular</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral pattern bombing</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total eyes</td>
<td>1</td>
<td>9</td>
<td>24</td>
</tr>
</tbody>
</table>

* Nine eyes with preoperative visual acuity of 6/6 or better
** Four eyes with pre-operative and progressive cataract

Of the 103 fellow eyes which were untreated, improvement by 1 line was shown by seven during the observation time. The preoperative visual acuity was maintained in 56; sixteen of these had vision 1/60 or worse from the start. Forty eyes showed deterioration of visual acuity (21 by 1 line, eight by 2 lines, two by 3 lines, three by 4 lines, and six by 5 lines—Snellen chart) (Table IV, overleaf).

Follow-up

We had no recurrence of macular oedema or vascular reactivation at the edges of treated target areas. In twelve cases second operations were deemed advisable (and performed):
two because of the appearance of a new hypoxic focus 8 months and 12 months respectively after the first session, in one because of a general increase in the retinopathy (6 months after the first session), and in nine because the foci originally demonstrated were not altogether or not adequately light-coagulated at the first session.

It was thought interesting to contrast the pattern of visual acuity change in the first, previously reported, group of forty patients (44 treated eyes) with the later addition to our clinical material of 72 patients (77 treated eyes). It was anticipated that, in view of increasing age alone, one would find a gradual shift towards deterioration of macular function. The analysis of visual changes did not, however, confirm this assumption: the earlier, 2 to 4 years follow-up group, did better than the later, 6 months to 2 years follow-up group (Fig. 6, opposite).

One may speculate that the full recovery of macular function after the elimination of twilight circulation areas around the macula and breaking down of a vicious circle of localized metabolic embarrassment may require a longer time even than 2 years.

Discussion

Of the 121 treated eyes, 112 retained their visual acuity or improved, half of them markedly, and nine became worse (four from preoperative progressive cataract). Of the 103 untreated eyes, 56 retained their visual acuity and seven slightly improved, whilst forty suffered deterioration of vision, half of them severe. These clinical observations allow us very little doubt as to the usefulness of our method of treatment. Moreover, the follow-up time extending up to 4 years demonstrated a widening gap between the fate of the treated v. the untreated eyes.

Considering only the patients who stayed in the paired-eye trial, elimination of the nine cases treated bilaterally leaves us with 103 patients whose worse eye was treated, the other having been left alone as a control. Two observations emerged from the analysis of the visual acuity change of this controlled group of paired eyes. The first applies to those eyes in which the visual acuity did not change, either in the treated or untreated group. Of the untreated eyes, for up to 2 years the visual acuity in about two-thirds remained unchanged (65 per cent.) but this figure was almost halved at the end of 4 years (35 per cent.), and these eyes mostly shifted into the "worse" category. As a result, the number of eyes which deteriorated had doubled after 4 years. Among the treated eyes about half (49.9 per cent.) remained unchanged up to 2 years. This figure was also halved at the end of 4 years (to 23.8 per cent.). However, in this group, half of those eyes showed improvement, bringing the overall "improved" figure after 4 years to 64.1 per cent. while only 6.6 per cent. showed deterioration, bringing the overall deterioration figure at the 4 years mark to 12.8 per cent. (Fig. 6).

Table IV  Visual acuity change in 103 untreated eyes (follow-up 6 mths to 5 yrs)

<table>
<thead>
<tr>
<th>Visual acuity</th>
<th>Improved</th>
<th>Same*</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lines</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No. of eyes</td>
<td>7</td>
<td>56</td>
<td>21</td>
</tr>
</tbody>
</table>

* Sixteen eyes with original visual acuity 1/60 or less
Pathogenesis and treatment of diabetic maculopathy

6mths to 2 years follow-up (64 eyes)
- Treated: 46.9%
- Untreated: 53.1%

6mths to 2 years follow-up (64 eyes)
- Treated: 7.8%
- Untreated: 92.2%

2 to 4 years follow-up (39 eyes)
- Treated: 64.1%
- Untreated: 35.9%

2 to 4 years follow-up (39 eyes)
- Treated: 51%
- Untreated: 49%

**FIG. 6** 103 paired eyes. Visual acuity changes in the short-term and long-term observation groups

**FIG. 7** 103 paired eyes. Overall visual acuity changes. Observation time 6 months to 4 years

The second observation comes from statistical analysis. The $\chi^2$ analysis of the change in visual acuity of the same paired-eyes group of 103 patients gave $P \ll 0.001$ (Table V, overleaf).

This means that there is much less than one chance in 1,000 that there is no difference between the fate of the treated and untreated eyes for this series. Fig. 7 contrasts the change in visual acuity of 103 eyes which stayed paired during the trial.

Encouraging results, apart from our own previous report regarding 44 eyes affected by maculopathy (Rubinstein and Myska, 1972), have also been published by Cheng, Blach, Hamilton, and Kohner (1972) regarding eighteen randomized patients with diabetic maculopathy and by Patz, Schatz, Gitteloson, and Ticho (1973) regarding 63 randomized cases affected by macular oedema.
Table V  $\chi^2$ comparison of treated and untreated eyes

<table>
<thead>
<tr>
<th>Visual acuity</th>
<th>Improved</th>
<th>Same</th>
<th>Worse</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>55</td>
<td>39</td>
<td>9</td>
<td>103</td>
</tr>
<tr>
<td>Untreated</td>
<td>7</td>
<td>56</td>
<td>40</td>
<td>103</td>
</tr>
</tbody>
</table>

$\chi^2 = 156.08 \quad n = 2 \quad$ From tables $P \ll 0.001$

Summary

It is submitted that a retinal hypoxic focus, if located in the vicinity of the macula, presents the basic pathogenic lesion underlying the development of diabetic maculopathy and determining its pattern. Conversion of these foci into anoxic scars by light coagulation would be expected to improve macular function or to arrest its further impairment. Based on this working hypothesis, 121 eyes (in 112 patients) affected by diabetic maculopathy were treated by light coagulation aimed at converting hypoxic retinal foci into inert scars. Routinely the better eye of the two was not treated and was used as a control. The operations were performed under sedation and local anaesthesia and as out-patient procedures. Follow-up time extended from a minimum of 6 months to 4 years. Of the treated eyes 53 per cent. showed improvement of visual acuity against only 4 per cent. which deteriorated (apart from four cases of preoperative progressive cataract). Of the control eyes, 6-8 per cent. improved and 38.9 per cent. deteriorated. Of the treated eyes, 38.8 per cent. including nine eyes with preoperative visual acuity below 6/60 remained unchanged; of the untreated eyes 54-3 per cent. remained unchanged. For the 103 paired eyes, $\chi^2$ statistical analysis demonstrated $P \ll 0.001$, a highly significant figure.

We wish to thank Dr. J. Marsters for his help with the statistical analysis.

References


——— (1971) Ibid., 91, 357

——— (1972) Brit. J. Ophthal., 56, 1
Pathogenesis and treatment of diabetic maculopathy.

K Rubinstein and V Myska

*Br J Ophthalmol* 1974 58: 76-84
doi: 10.1136/bjo.58.2.76