Communications

Simple diabetic retinopathy

Evolution of the lesions and therapeutic considerations

J. H. DOBREE

St. Bartholomew's Hospital, London

The name Simple (or Exudative) Diabetic Retinopathy includes a variety of diabetic changes, in particular, lipid exudates, microaneurysms, and haemorrhages. The term specifically excludes cases in which new vessel formations are present: Proliferative or Malignant Diabetic Retinopathy (Burditt, Caird, and Draper, 1968). Simple diabetic retinopathy shows a marked tendency to be symmetrical and to involve the posterior poles of the eyes; for this reason the term Diabetic Maculopathy is sometimes applied. The lipid exudates constitute the most obvious clinical sign, but the more fundamental lesions are small islets of pathological capillaries in which microaneurysms are the most easily observed elements. These changes in the minute vessels usually precede the lipid changes and it is the deposition of lipid and oedematous changes in the macular area which cause the risk of the loss of central vision. The present investigation has two aims in view:

- (1) To examine the spontaneous changes in exudates and foci of capillary damage which take place over a period of several years, for only by a knowledge of these changes can the effect of therapy be assessed.
- (2) To determine if capillary lesions in any particular anatomical areas could be shown to have a particularly adverse effect in the formation of exudates or oedema in the macular area.

This investigation has been made retrospectively by the examination of serial fundus photographs taken over several years of patients suffering from bilateral simple diabetic retinopathy of varying degrees of severity.

Clinical material

Fifty eyes of 25 patients have been selected and studied by serial fundus photographs for periods of between 2 and 7 years. The average time of observation of each eye is 3.6 years and the interval between successive photographs rather less than 6 months. The general data (age, sex, duration of diabetes, etc.) are given in Table I and the details of the photographic observations in Table II. In order to confine the observations to the retinal changes, only eyes with clear media were included in this study. Some of the patients were included in a previous study as cases or controls in an investigation of the effects of a corn-oil diet (King, Dobree, Kok, Foulds, and Dangerfield, 1963).

Ophthalmoscopic and other examinations were made at each visit of the patient, but the photographs form the basis of the data obtained. Although the resolution of the fundus camera is greatly inferior to that of the human eye, a permanent record which can be examined and re-examined and any lesion traced forwards or backwards in time is superior to purely visual records and is less liable to observer error.

Methods of examination

At the initial examination or early in the series most of the posterior half of each fundus was photographed by the Zeiss fundus camera to cover the following seven fields:

- The disc as centre.
- The four main groups of vessels for about 25° beyond the disc.
- The disc and macula.
- The macula as centre.

Subsequent routine pictures always included the posterior pole, that is within the area bounded by the superior and inferior temporal vessels above and below with the disc medially and an area of retina about 2 disc diameters lateral to the disc, and any other areas in which pathological changes were taking place.

The number of slides taken of each patient is considerable, ranging from 35 (Case 23) to 162 (Case 4), so that it is relatively easy to secure identical fields for comparison throughout any given series.

Comparison of serial slides was made directly in all cases. An additional technique which provided valuable data was to trace the lesions from a retro-illuminated screen on to transparent polythene sheets. It was possible by this means to establish the permanence of small groupings of capillary changes over long periods and at the same time to record the waxing and waning of the lipoid deposits. This technique was used in 27 eyes (54 per cent. of the series), see Figs 1a and 1b (opposite).

Table I Sex and age of 25 patients studied

Case no.	Sex	Age (yrs)	
		At start of trial	At onset of diabetes
1	M	64	48
2	M	60	43
3	F	61	50
4	F	42	20
5	F	54	51
6	F	67	48
7	F	66	63
8	F	61	57
9	M	56	49
10	M	69	?
11	F	64	62
12	F	57	57
13	F	59	43
14	M	51	51
15	M	52	49
16	F	66	?
17	F	68	52
18	F	53	43
19	F	60	56
20	F	64	55
21	M	57	49
22	F	67	55
23	M	51	31
24	M	49	29
25	M	48	27

Findings

(I) Foci of pathological capillaries (Table II, overleaf)

(i) Appearance

Microangiopathy in simple diabetic retinopathy occurs as small scattered foci lying mainly at the posterior pole. These areas are most easily identified ophthalmoscopically by small clusters of microaneurysms, but varicose capillaries and small punctate haemorrhages also enter the picture (Ashton, 1949), so that the foci appear on the photographs as collections of small red dots, the largest covering an area up to one-eighth of the area of the disc in extent (Figs 1a and 1b). Depending on the leakage from the damaged capillaries, a varying amount of oedema is also present.

(ii) Numbers of foci per fundus (Table II)

The foci varied in number from 0 (3 cases) to 8 (average 2.8) per eye. No focus was accepted unless it appeared in at least two successive photographs and care was taken to identify some of the smaller aneurysmal clusters by serial tracings (see method above). It must be clearly understood that only the larger foci of capillary damage can be identified by colour fundus photographs, so that these figures could easily be doubled if all those observable by ophthalmoscopy were included.

FIG. 1a Photograph of left fundus on May 11, 1965, showing foci of pathological capillaries (A, B, C) and surrounding exudates

M = Macula

FIG. 1b Same fundus as in Fig. 1a, showing the effect of superimposing four photographs taken between January 14, 1964, and May 3, 1966. The green areas indicate the total area of retina in which lipid exudate has occurred during this period. The foci A, B, C of Fig. 1a appear in each photograph and these foci remain free from lipid deposits

(iii) *Duration of foci* (Table II)

The length of time that groups of pathological capillaries could be identified is given in Table II, which indicates the longest time for which any one focus could be traced. Some foci proved to be remarkably stable and in ten eyes were visible in successive photographs for 4 years and upwards.

(iv) *Location of foci of pathological capillaries*

A striking feature of the distribution of the foci was the large number which was found in a

Table II Ocular data in 25 patients

Case no.	Eye	Observation		Visual acuity		Pathological capillary foci			Size of macular plaques (in disc areas)
		Duration (yrs)	Number	Initial	Final	Number	Duration (yrs)	Position of paramacular foci (in disc diameters from centre)	
1	R	2.2	3	6/18	6/60	4	2.2	lat. 1.0	0.5
	L	2.2	4	6/18	6/24	4	2.2	lat. 0.5	0.25
2	R	3.4	8	Counting fingers	3/60	—	—	—	2.5
	L	3.4	11	Counting fingers	6/60	4	1.5	sup.-med. 0.5	0.25
3	R	5.0	6	6/24	6/60	1	1.5	—	0.25
	L	6.7	7	6/24	5/60	2	6	lat. 1.0	2.0
4	R	7.0	12	6/9	6/9	2	5	lat. 1.0	0.125
	L	7.0	10	6/60	6/9	1	5	lat. 1.0	0.5
5	R	4.1	6	6/9	6/24	1	1+	lat. 1.0	0.125
	L	4.1	6	6/60	6/60	3	1+	lat. 0.5	0.5
6	R	2.5	5	6/24	6/24	6	2.5	inf. 0.25	—
	L	2.5	5	6/18	6/24	4	2.5	inf.-lat. 1.0	0.05
7	R	2.3	6	6/9	6/18	3	1	lat. 1.0	0.5
	L	2.3	7	6/12	6/60	2	1.7	lat. 0.5	0.25
8	R	3.3	7	2/60	2/60	—	—	—	0.5
	L	3.9	8	6/18	6/18	3	4	(1) lat. 1.0 (2) lat. 0.5	—
9	R	5.3	7	6/60	Hand movements	1	1.3	Inside plaque	2.0
	L	5.1	8	6/60	6/60	2	4.9	(1) sup. 1.0 (2) lat. 1.0	1.25
10	R	2.3	5	6/12	6/24	3	1.3	inf. lat. 0.5	—
	L	2.3	4	6/60	6/60	2	1.3	—	—
11	R	2.5	8	6/9	6/9	2	2	—	—
	L	2.5	6	6/24	6/60	3	4.3	(1) lat. 0.5 (2) inf. 0.75	—
12	R	3.9	7	3/60	6/24	6	3.7	(1) sup.-lat. 1.0 (2) lat. 1.0	1.0
	L	3.9	6	6/9	6/36	6	2.3	(1) lat. 0.5 (2) lat. 1.0	0.5
13	R	3.3	7	6/6	6/9	2	3.3	(1) lat. 0.25 (2) lat. 1.5	0.1
	L	3.8	10	6/6	6/6	3	2.3	inf.-lat. 0.25	0.2
14	R	2.0	6	6/9	6/6	3	2	—	—
	L	2.0	6	6/5	6/5	2	1.3	sup.-lat. 0.25	0.05
15	R	5.5	10	6/18	6/9	2	1.8	lat. 0.75	0.1
	L	4.5	13	6/6	6/9	4	4.3	lat. 1.0	0.2
16	R	4.4	11	6/36	6/36	8	4.4	(1) inf. 0.5 (2) lat. 1.50	1.5
	L	4.4	7	6/24	6/24	2	2.2	inf.-lat. 0.5	0.125
17	R	2.1	8	6/24	3/60	3	2.0	(1) lat. 0.50 (2) lat. 1.0	—
	L	2.1	9	6.24	6/24	3	2.0	lat. 1.0	—
18	R	4.7	8	6/9	6/24	3	4.0	lat. 1.0	—
	L	4.3	6	6/60	6/60	—	—	—	0.25
19	R	3.0	9	3/60	6/36	3	0.8	lat. 1.0	0.50
	L	3.0	10	Counting fingers	Counting fingers	2	1.0	lat. 1.0	4.0
20	R	3.5	8	6/60	6/60	2	3.7	(1) sup.-lat. 0.25 (2) inf.-lat. 0.25	0.125
	L	3.5	8	6/24	6/18	3	3.1	—	0.25
21	R	2.7	6	6/9	6/6	4	2.7	(1) lat. 0.5 (2) lat. 1.0	—
	L	2.7	7	6/6	6/6	2	1.4	inf. 0.5	—
22	R	4.1	11	6/60	6/36	3	4.0	(1) lat. 1.0 (2) med. 0.25	0.75
	L	3.5	12	6/36	6/36	5	0.8	lat. 0.25	0.25
23	R	2.0	7	6/6	6/6	1	2.0	lat. 1.0	—
	L	2.0	5	6/6	6/9	1	2.0	sup.-lat. 1.0	—
24	R	3.8	8	6/6	6/6	3	3.7	lat. 1.0	0.125
	L	4.3	11	6/6	6/9	4	3.8	lat. 0.50	0.125
25	R	6.7	11	6/12	6/9	6	6.4	inf.-lat. 1.50	—
	L	6.7	8	6/9	6/6	1	6.4	inf. 0.25	—

(1) Visual acuities taken to lowest correct line on Snellen chart

* Foci of pathological capillaries measured from centre of macula within a radius of 1.5 disc diameters

small area lateral to the macula. Out of a total of 140 foci, 44 (31.4 per cent.) lay on the lateral side of the macula (including the supero- and infero-temporal positions) and within $1\frac{1}{2}$ disc diameters of it.

This concentration of microaneurysmal clusters and varicose capillaries in this small area lateral to the macula is thought to be connected with the anatomical distribution of the vessels; for, in the region lateral to the macula, there is a confluence of small arterioles and venules from the main superior and inferior temporal vessels and these small twigs have vascular territories which interdigitate across the horizontal raphe of the retina (Fig. 2). In contrast, medial to the macula and above and below it, the small vessels run radially towards the parafoveal zone.

FIG. 2 *Vessels surrounding the macula of the left eye. Note the confluence of vascular territories across the horizontal raphe lateral to the macula. Note focus of pathological capillaries just lateral to macula*

F = Fovea

Apart from the lateral macular congregation, pathological capillary foci are fairly widely scattered over the posterior fundus. They are noticeably away from the main vascular trunks. This distribution is interesting in connexion with another investigation currently reported (Taylor and Dobree, 1970), in which we have studied the location of new vessel formations from similar photographic records of patients with proliferative diabetic retinopathy. In this group the new vessel formations which were of sufficient size to be seen on fundus photographs were almost entirely confined to the area of the disc and main vascular branchings.

(II) Lipoid exudates

(1) FORM OF EXUDATES

In a previous paper (King and others, 1963), three forms of lipoid deposit were described:

- (a) clusters of small flecks of lipoid material.
- (b) deposits in the form of large and small rings.
- (c) plaques of lipoid material at the posterior pole often involving the macula.

The present survey has confirmed the previous findings and added new information on the relationship of exudates to the foci of pathological capillaries.

(a) *Features of cluster forms*

Small fleck-like deposits of lipoid are arranged in small clusters up to one disc area in extent. There is often evidence of preceding capillary pathology in the vicinity. These are the most transitory forms of exudate and often appear and disappear in as short a time as 4 months.

(b) *Features of ring forms*

Ring exudates exist in all sizes from about one-sixth of a disc area to large wreath-like aggregations several disc diameters across. For the purpose of this paper small rings are defined as those having an outer limit less than one disc area and large rings as those of one disc area or more.

The number of ring forms found was considerable; 93 small rings (average 1.9 per fundus) and 27 large rings (average 0.54 per fundus) were identified.

Serial observations and especially tracings often reveal unsuspected ring forms, for if an arc of a ring is present on one slide the observations before and after frequently supply further arcs to complete the ring.

The general pattern of the formation of rings, which appears to be the fundamental form of lipoid deposit, is that of a continuous process of deposition and re-absorption so that any one slide may show several rings in varying stages of development. The duration of the rings is variable and depends largely on the amount of lipoid originally laid down. The smallest rings may appear and disappear within 6 months and those about the size of a disc take 2 to 3 years to form and disappear. The largest wreath-like rings are especially stable and in two eyes were found to persist for over 4 years.

Houston and Wise (1957) noted that numerous ring forms contained a central cluster of microaneurysms. This survey supports their observations. Out of 93 small rings, 61 (65.6 per cent.) had aneurysms or other evidence of pathological capillaries situated in their central areas. With regard to the 27 large rings, fifteen (55.5 per cent.) had areas of capillary pathology included, several foci being present inside some of the larger rings.

(c) *Lipoid plaques at posterior pole*

In 35 out of the fifty eyes examined (70 per cent. of cases) plaque-like lipoid deposits either covered or involved the macular area. These varied in size from massive confluent deposits some 2 to 3 disc diameters across to small aggregations about one-tenth of a disc area in extent. They were sometimes rounded masses centred at the macula or arranged in a somewhat stellate form consisting of a number of smaller deposits. An attempt has been made to record their greatest extent in terms of disc area (Table II). Their duration depends largely on the mass of lipoid material involved and the largest persist for over 5 years. Without exception the plaques varied in size throughout the period of observation, and in twenty out of the 35 cases periods of both increase and decrease were noted.

A macular deposit is often part of a ring formation (Welsh, 1968) and often forms the largest deposit of that ring. This was found in nine (18 per cent.) of the eyes. Deposition of lipoid in the macular area is probably related to the fact that the macular and paramacular tissues readily imbibe fluids in many pathological conditions and there appears to be a preferential "pooling" of lipoid here. It was not possible to make out any close association between foci of capillary pathology and macular plaques because of the frequency of foci in the paramacular area. Thus, out of the 35 eyes showing macular deposits, 27 (77.1 per cent.) had one or more foci within 1 disc diameter of the macula, and of the fifteen eyes without deposits thirteen (86.7 per cent.) had similar foci. On the other hand

it must be remembered that the period of observation (average 3.6 years) represents only a fraction of the time of duration of the retinopathy.

(2) LATE MACULAR CHANGES

Deposits of cholesterol crystals were left as residues after large macular plaques in two eyes (4 per cent.). A marked macular pigmentation following resolution of a plaque was seen in six eyes (12 per cent.) and a connective tissue scar in a further case. These findings emphasize once again an important observation in our previous study (King and others, 1963), namely, that even after complete absorption of a macular plaque, permanent damage to the macular tissues is usual.

(3) APPEARANCE AND DISAPPEARANCE OF LIPOID DEPOSITS

It has long been known that there is a continuous process of deposition and absorption of lipid material in a diabetic fundus, but the full extent of this was not recognized until tracings of the lipid deposits were superimposed one over the other and the total area of retina involved was charted (Figs 1*a* and 1*b* show an example, but this is by no means the most extensive deposition in the series). The foci of pathological capillaries were also charted and these areas remained free from lipid while the tissue surrounding them became heavily infiltrated by deposits either in the form of rings or as more isolated masses. Examination of the edge of an area of lipid deposition either in the macula or elsewhere usually provided information whether lipid was being laid down or absorbed. In the former case the contours are rounded (map of Africa appearance) and in a regressive phase there are extensive "bays", "inlets" and "off-shore islands" (map of N. America appearance).

(4) MACULAR OEDEMA

Oedema of the macula was a common finding throughout the series. In the case of the larger lipid deposits on and around the macula, oedema is especially marked in the early stages of their formation. Fundus contact lens examination in these cases reveals that the retina may be swollen to two or three times its normal thickness. Macular oedema of all degrees may be found with or without lipid deposits and in one case cyst formation occurred. The fluorescein studies of Gass (1968) in exudative retinopathy are particularly illuminating in this connexion. He has demonstrated that in these cases the vascular leakage is largely confined to the paramacular region on the temporal side of the macula.

(5) RELATION OF MACULAR CHANGES TO VISUAL ACUITY

There is a broad correlation between the size of a macular deposit at its greatest development and the loss of central vision. Fourteen of the fifty eyes had macular lipid deposits of half a disc area or greater. These are shown in Table III (overleaf). It will be seen that in six eyes with a macular plaque greater than one disc area the best vision was 6/36 and in the remaining five eyes the best vision was 6/60 or below. Of the eight eyes with a plaque between half and 1 disc area in extent, one eye achieved 6/9 vision and the remainder between 6/18 and 6/60.

Seven of the fourteen eyes showed a complete or almost complete clearing of lipid in the macular and paramacular area. Four of these eyes showed a marginal improvement in the greatly reduced vision, one deteriorated, and two were unchanged. This failure to recover vision after the absorption of macular lipid thus occurs in cases of spontaneous clearance and in cases in which the disappearance of lipid is associated with treatment by

corn-oil (King and others, 1963) and by Atromid (Duncan, Cullen, Ireland, Nolan, Clarke, and Oliver, 1968).

Four eyes (in two patients) had massive macular oedema with minimal lipid deposition (Table III). When the oedema subsided a considerable degree of macular pigmentation was present. One of these four eyes showed a striking improvement in vision, but there was little change in the remainder.

Table III *Visual acuity in severe maculopathy*

<i>Macular lesion</i>	<i>Eye</i>	<i>Visual acuity</i>		<i>Greatest size of plaque in macular area (d.a.)</i>	<i>Final state of macula</i>
		<i>Initial</i>	<i>Final</i>		
Lipoid plaques	R	6/18	6/60	0.5	0.25 d.a. lipoid
	R	Counting fingers	3/60	2.5	Macular pigmentation—no lipoid
	L	6/24	5/60	2.0	Central fibrous scar—no lipoid
	L	6/60	6/9	0.5	No lipoid
	R	6/9	6/18	0.5	0.5 d.a. lipoid
	R	2/60	2/60	0.5	0.5 d.a. lipoid
	R	6/60	Hand movements	2.0	0.5 d.a. lipoid
	L	6/60	6/60	1.5	0.5 d.a. lipoid
	R	3/60	6/24	1.0	No lipoid
	L	6/9	6/36	0.5	0.25 d.a. lipoid
	R	6/36	6/36	1.5	No lipoid
	R	3/60	6/36	0.5	No lipoid
	L	Counting fingers	Counting fingers	4.0	No lipoid
	R	6/60	6/36	0.75	0.25 d.a. lipoid
Massive oedema without lipoid deposit	R	6/12	6/24	—	Macular pigmentation
	L	6/60	6/6	—	Macular pigmentation
	R	6/24	6/60	—	Macular pigmentation
	L	6/24	6/24	—	Macular pigmentation

d.a. = disc area

The change in visual acuity for all patients during the period of observation is given in Table II, which shows that the visual deterioration is very slow and supports the findings in the large series of cases reported by Caird and Garrett (1963). A comparison between the initial and final visual acuities demonstrates that a diminution in visual acuity in exudative retinopathy is usually permanent.

(III) Pathological veins and arterioles in exudative diabetic retinopathy

On one occasion at least, routine pictures of the retinal vascular tree as far as the equator were taken in every case. These can be compared with the vascular trees of 112 cases of proliferative retinopathy which were recently screened to determine the frequency of

certain physical signs in that condition (Dobree, 1968b). In the proliferative series venous calibre abnormalities were common, whereas in the exudative group they were found only in the two eyes of Case 2. Pathological arterioles, which appeared as white lines on the photographs, in which the walls were replaced by connective tissue and the lumina were extremely narrow or absent (Davis, Myers, Engerman, de Venecia, and Magli, 1968) were found in 17.9 per cent. of cases of the proliferative series and in only one of the exudative series here reported.

In another study (Taylor and Dobree, 1969), it was found that the "true" new vessel formations in proliferative diabetic retinopathy are related to the larger retinal vessels, whereas the present study shows that the areas of capillary pathology are found mainly at the posterior pole and are not related to the larger vessels. This suggests that an essential difference, if not *the* essential difference, between simple and proliferative diabetic retinopathy lies in the fact that in simple diabetic retinopathy the angiopathy affects capillaries and in proliferative diabetic retinopathy the larger retinal vessels are involved.

(IV) Therapeutic considerations

From the facts that many of the ring forms of exudates surround foci of capillary damage and that serial tracings demonstrate the formation of plaques of exudates related to other foci, there can be little doubt that there is a direct relationship between the two.

Maumenee (1968) reviewed the controversial issue whether retinal lipid deposits are due to neuronal degeneration consequent on capillary damage or on leakage from the damaged capillaries, and concluded that the fundamental pathological change is capillary leakage. The fluorescein studies of Gass (1968) already mentioned support this view. In either case the loss of vision in simple diabetic retinopathy is caused in the main by the deposition of lipid and oedema in the macular area. Meyer-Schwickerath and Schott (1968) and Wessing and Meyer-Schwickerath (1968) reported favourably on the effects of light coagulation on the lesions of simple diabetic retinopathy, and Welsh (1968), describing the effect of photocoagulation of "aneurysmal and neovascular areas" in the centre of lipid rings, reported improvement, sometimes dramatic, in those cases in which the ring involved the macula. Maumenee (1968), in cases of Coats's disease in which the lipid deposits are similar but the leakage more copious, also reported marked improvement after light coagulation.

With a knowledge of the natural history of the disease, the following rationale is suggested:

- (1) A case showing maculopathy should be reviewed by serial fundus photographs at as early a stage as possible in the disease.
- (2) As the progress is very slow it is unnecessary to take immediate action on all areas of capillary damage as many of these do not have associated oedema or lipid deposits and unless related to the macula such changes have little effect on vision.
- (3) The most careful watch should be kept on capillary lesions just lateral to the macula and, should fluorescein studies or other evidence suggest macular involvement, these should be eradicated before extensive macular deposits form as the resultant visual loss is likely to be permanent.
- (4) In the light-coagulation of such areas in the vicinity of the macula, *special caution should be exercised in limiting the extent of the coagulations* so as to avoid unnecessary damage to the arteriolar supply or venous drainage of the macular area. The writer has already seen two cases complicated by macular oedema caused by failure to observe this principle.

(5) As simple diabetic retinopathy runs a protracted course, the patient must be kept under constant review by serial photographs and fluorescein studies. Several coagulations spread over a long period of time may be indicated.

Summary

(1) The relationship between lipid exudates and foci of pathological capillaries has been studied in fifty eyes over periods varying from 2 to 7 years.

(2) By superimposing tracings of foci of pathological capillaries and lipid exudates, it has been shown that the capillary foci are very stable and that the lipid exudates either surround them in ring forms or appear as clumps of deposit related to them. There is preferential "pooling" of lipid in the macular area.

(3) Almost one-third of the foci of pathological capillaries was found in a small area just lateral to the macula.

(4) In general the foci of capillary damage of simple diabetic retinopathy lie in a different region of the retina from the new vessel formations of proliferative diabetic retinopathy.

(5) The permanence of the loss of vision after lipid deposition or oedema of the macular area is stressed.

(6) With a knowledge of the spontaneous evolution of the lesions of simple diabetic retinopathy, a rationale of treatment by direct application of light energy to selected foci of pathological capillaries is suggested.

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