CHOLESTEROL

I

" Corn Oil " Diet in Diabetic Retinopathy

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This paper concerns the preliminary results of an investigation of the effect of a diet low in animal fat and moderately high in vegetable fat on the progress of diabetic retinopathy. This investigation has been undertaken at Addenbrooke's Hospital, in collaboration with Mr W. Foulds, and at St Bartholomew's Hospital in London by Dr R. C. King and Mr J. Dobree.

Insulin, antibiotics, and intravenous electrolyte infusions have entirely changed the prognosis of severe infections and of coma in diabetes mellitus. As a result, greater numbers of young diabetics are now able to survive for 25 years or more, but, in doing so, they become increasingly liable to the development of retinopathy. It has been estimated in the U.S.A. that over 75 per cent of diabetics of more than 15 years' standing show some evidence of retinopathy.

The pathological features of retinopathy suggest that it is essentially a degenerative process, affecting both the vascular and the nervous elements of the retina—(Bloodworth, 1962).

The vascular changes are patchy, and affect both the superficial and the deep capillary networks of the retina. They consist of irregular variations in the calibre of the capillaries, with varicose dilatations or abrupt contractions of all elements of the capillary wall, which result in attenuation of the lumen for variable distances. Secondly, the better known thin-walled aneurysmal dilatations of the capillary wall are associated with degeneration of the pericytes normally present in the basement membrane of the capillary wall and with rupture of strands of the basement membrane. These thin-walled aneurysms are filled with blood initially. Hyaline carbohydrate-rich material is subsequently deposited on the inner surfaces of the aneurysms, and may eventually fill them, so obliterating their lumena. The retinal veins tend to become dilated, and eventually show varicose changes.

Changes in the nervous elements are also very important, but are not so well known. Degeneration of the neurones and their nerve fibres results in the liberation of breakdown products rich in protein, carbohydrate, and lipid. These accumulate in the deeper layers of the retina, where they may be phagocytosed to a varying extent by microglia, or may ultimately undergo hyaline change. They corres-

pond to the waxy exudates seen ophthalmoscopically. A secondary gliosis develops in areas of neuronal atrophy.

Haemorrhages occur intermittently. Those appearing in the deeper layers of the retina are circumscribed by the pressure of the surrounding nervous tissue, and are rounded in outline. Superficial haemorrhages are less well circumscribed, and appear flame-shaped. Large haemorrhages may occur and rupture into the vitreous; they resorb slowly and give rise to granulation tissue, known clinically as retinitis proliferans. Neo-vascularization may also occur in the areas of neuronal atrophy. It is thought to be a response to a vaso-formative factor which accumulates in areas of low oxygen tension.

It is still uncertain whether the vascular changes occur first and give rise to the neuronal damage as a secondary phenomenon, or whether a metabolic defect gives rise to neuronal damage primarily and is accompanied by the vascular changes.

Clinically, retinopathy may be found soon after the discovery of diabetes and may even be the presenting feature. In the majority of instances, however, it develops in long-standing disease, especially if poorly controlled. In the early stages, clusters of minute, red dots appear in crops, last for a variable period of months, turn yellow as they fill with the hyaline deposit, and subsequently fade or are replaced by white dots. Small, discrete, waxy exudates then appear, often around a haemorrhage. They may fade, or may enlarge, coalesce and form large masses, particularly in the region of the macula. Despite apparent spontaneous remissions, which may occur during the course of the disease, the overall change in any given case is steadily progressive, and sooner or later becomes associated with loss of visual acuity. A massive haemorrhage may occur at any time during the course of the disease. It is associated with the sudden onset of varying degrees of blindness, and may be followed by the appearance of retinitis proliferans.

Treatment of diabetic retinopathy has in the past been very unsatisfactory. Joslin has claimed that rigid control of the diabetes prevents the onset of retinopathy, although it does not halt the progress of established disease. Diabetic retinopathy may improve during the development of Simmonds' disease. It may be exacerbated by pregnancy which is associated with excessive amounts of pituitary somatotrophic hormone, or by steroid therapy. Because of these observations, adrenalectomy and more recently hypophysectomy have been tried, and have proved to be of benefit in some cases. These operations carry a definite operative mortality, and patients are left with two endocrine deficiencies, which increase the difficulty of clinical management. Enthusiasm for these methods of treatment

is therefore waning. A variety of other therapeutic approaches, including treatment with vitamin B_{12}, has been unsuccessful.

Diabetes mellitus is characterized by a whole spectrum of biochemical derangements. This includes, not only the well-known defect of glucose utilization, but defective synthesis of protein and fat. The defect in fat synthesis results in an almost complete loss of ability to synthesize fatty acids from " active " acetate and its precursors such as glucose. The increased dependence on the breakdown of fatty acids from adipose tissue to satisfy the energy requirements of the body results in raised levels of free fatty acids and of triglyceride in the blood, together with raised levels of beta lipoprotein which acts largely as a carrier for triglyceride. For various reasons the excessive amounts of fatty acids so formed cannot be oxidized quickly enough to carbon dioxide and water in the normal way via the Krebs cycle, so that a proportion is shunted into the formation of ketone bodies. Cholesterol synthesis seems to be increased.

An association between vascular disease and elevated levels of plasma lipids appears to be well established now, and seems to be related particularly to a high intake of animal fat in the diet. It is known that lipaemia is associated with abnormalities of blood coagulation and of fibrinolysis. The chylomicra in lipaemic blood increase the viscosity of blood and may affect the flow of blood in small vessels. The relationship of these observations to the development of retinopathy in diabetes mellitus is, however, completely speculative at present. Nevertheless, Bloor showed in 1916 that the increased plasma lipid levels in diabetes paralleled the severity of the condition, and that treatment by calorie restriction combined with marked reduction of dietary fat intake reduced the plasma lipaemia. In 1945, Kempner observed a progressive improvement in the retinopathy of two hypertensive patients who happened to have diabetes as well, and who were being treated with his rice diet. These findings were confirmed in 1959 by Van Eck, who reduced the animal fat intake of a small group of diabetic patients to 20 grams per day. Five patients showed moderate improvement in retinopathy, three showed a slight improvement, and two showed no improvement.

A diet containing only 20 G. of fat per day is very impalatable. It can be made more appetizing by supplementing it with vegetable fat, and this does not impair its effectiveness in lowering plasma lipid levels, as has been shown by Rhoads and Barker (1959) and by Schroepfer, Friedrich and Goetz (1960).

We have investigated the effect of a diet containing 20—25 G. of animal fat together with 60 G. of vegetable fat. In order to get the animal fat content down to this level, the protein intake had to be

TABLE I

SERUM LIPIDS MG. PER CENT

	Total lipid	*Total fatty acid*	*Total cholesterol*	*β lipid*	*β cholesterol*
R.L. (male)					
17.12.60	570	410	220	340	140
4. 2.61	520	390	182	300	120
3. 3.61	615	348	186	344	124
25. 3.61	500	348	187	250	102
6. 5.61	520	370	180	280	110
3. 6.61	520	360	170	290	110
1. 7.61	470	280	160	260	96
E.L-D (female)					
3.12.60	750	620	280	640	240
7. 1.61	770	580	260	580	220
10. 6.61	860	590	290	640	250
12. 8.61	835	560	305	630	260

The retinal appearances were assessed by serial fundal photographs, and the hanges are tabulated below (table II).

TABLE II

RETINAL APPEARANCES

	Definitely improved	*Original lesions better Fresh lesions at different sites*	*Definitely worse*
A. Control			
Predominantly exudative lesions	0	6	7
Vascular lesions progressing to retinitis proliferans ..	0	0	6
Total number of cases ..	0	6	13

B. Treated Cases	*Improved*	*Worse*
St. Bartholomew's Hospital	8	1
Addenbrooke's Hospital	5	2
Total number of cases	13	3

reduced to approximately 70 G. per day. The vegetable fat consisted of a range of commercial products reasonably well tolerated by the patients. The carbohydrate intake was adjusted to achieve optimal body weight. Treatment so far has continued for periods varying from 9 to 24 months.

Serum lipid studies were undertaken in an attempt to assess the degree of adherence to the diet, and were carried out by Dr Dangerfield at the North Middlesex Hospital in London. Results from two patients are listed in table I. The first set of values was obtained from a patient who had adhered conscientiously to his diet. The second set was obtained from a control patient who had been left on her normal diet. Lipid values from some of the patients formed a variety of intermediate patterns, which, it has been assumed, indicate varying degrees of adherence to the diet.

One of the treated patients showing deterioration was a commercial traveller who was unable to adhere strictly to the diet. Another worked in a canteen and admitted to not adhering to the diet. The third was an elderly obese diabetic, who insisted that she had adhered to the diet, but whose weight and serum lipids remained unchanged.

Our experience so far suggests that a diet low in animal fat and supplemented with a moderate amount of vegetable fat, if adhered to, is associated with improvement in the haemorrhages and exudates in diabetic retinopathy. In some cases, visual acuity remains impaired, despite an improvement in the fundal appearances, and is presumably a legacy of past neuronal damage. This suggests that the earlier these patients are treated, the better the prognosis is likely to be. In this connection, the trial being carried out in diabetic children at Birmingham may prove to be of very great interest (Salt, Wolff, Nestadt and Lloyd, 1960). Further study of larger numbers of adult patients is also necessary.

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