DIABETIC RETINOPATHY AND CYANCOBALAMIN (VITAMIN B₁₂)*

A PRELIMINARY REPORT

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THE work of Ballantyne and Loewenstein (1943, 1944) served to clarify an understanding of diabetic retinopathy. Their findings have been amply substantiated by subsequent workers (Friedenwald, 1948; Ashton, 1950). A connexion between this condition and the Kimmelstiel-Wilson disease has also become established. More recently there is some evidence to implicate the adrenal cortex in the pathogenesis of the complex (Becker, 1952). Clinically, diabetic retinopathy and the Kimmelstiel-Wilson disease appear to be aggravated by the administration of ACTH in severe infections and during pregnancy: conditions which are all associated with increased adrenal cortical activity. Furthermore, the glomerular nodules typical of the Kimmelstiel-Wilson disease have been noted in rabbits after the administration of cortisone (Rich, Berthrong, and Bennett, 1950). In addition, a relationship between vitamin B₁₂, diabetes, and the adrenal cortical hormones has been postulated (Becker, Lang, and Chow, 1953) and animals experimentally deficient in vitamin B₁₂ have been reported to exhibit hyperglycaemia.

Skeggs, Nepple, Valentik, Huff, and Wright (1950), microbiologically measuring the amount of vitamin B₁₂ in 8-hour urinary specimens obtained from diabetic patients who had been given an intramuscular injection of a test dose of 50 µg of vitamin B₁₂, found very marked excretory differences between patients with and without retinopathy. Compared with a normal non-diabetic value of 9.6 gamma excretion, 22 patients with retinopathy had an excretion average of 19 gamma; thirteen diabetics without retinopathy excreted an average of 4.2 gamma, and it is claimed that the marked difference in the fraction excreted provides a clinical test for the presence or absence of retinopathy in the diabetic. These findings are presumed to indicate an increased adrenal cortical activity in the presence of retinopathy.

Vitamin B₁₂ has similarly been reported to be beneficial in the treatment of the diabetic neuropathies (Sancetta, Ayres, and Scott, 1951) and some interest has been taken in establishing a relationship between the presence of neuropathy and retinopathy in diabetics. It has been stated from the Johns Hopkins Hospital that over 90 per cent. of all diabetic neuropathies

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had, in addition, a retinopathy, and if vitamin B₁₂ deficiency is responsible for the diabetic neuropathic condition it is perhaps permissible to postulate that the diabetic with retinopathy is also depleted of vitamin B₁₂, at any rate more so than the non-retinopathic diabetic.

It is conceivable that diabetes and adrenal cortical hormones act through a deficiency in vitamin B₁₂ or through an inability to metabolize some steroids in the absence of B₁₂.

Becker, Allen, Winter, Maengwyn-Davies, and Friedenwald (1954) state that a deficiency of vitamin B₁₂ is not in itself sufficient to produce diabetic retinopathy or Kimmelstiel-Wilson disease, because this vitamin failed to prevent the cortisone-induced renal lesion in experimental rabbits, some of the animals showing lesions despite massive doses of vitamin B₁₂. On the other hand, the incidence of cortisone-induced renal lesions in rabbits was markedly increased by the omission of vitamin B₁₂ from their diet. The authors also state that severe deficiency of vitamin B₁₂ in rats did not produce renal lesions comparable to those in the Kimmelstiel-Wilson disease. A diagnosis of the Kimmelstiel-Wilson syndrome outside the *post-mortem* room is largely clinical conjecture.

Chow, Rosen, and Lang (1954) compared the vitamin B₁₂ serum levels in diabetic retinopathy and gave methods of estimating and determining the activity of B₁₂ in serum. They summarized their findings by presenting data to demonstrate that the serum levels of B₁₂ activity in diabetics with or without retinopathy are widely different, those in patients with retinal lesions being much higher than in patients without retinopathy. It seems clear that diabetics who have developed retinopathy handle their vitamin B₁₂ quite differently from diabetics without retinopathy, who seem unable to retain the normal portion of a test dose of vitamin B₁₂ and at the same time have higher levels of this vitamin in the peripheral blood. These workers think it impossible to escape the conclusion that vitamin B₁₂ is somehow fundamentally involved in the pathogenesis of diabetic retinopathy. Injection of this vitamin in animals deficient of it is said to correct the hyperglycaemia produced by a glucose tolerance test.

It would, therefore, seem reasonable to treat diabetics who have retinopathy with large doses of vitamin B₁₂. This has been done and an interim report on the results is given herewith.

Method

From a large Diabetic Clinic a cross-section of controlled cases with retinal changes was selected, an attempt being made to include varying ages and differing degrees of retinal pathology. In each case a careful clinical examination of both fundi was carried out and a note was made of all changes present. Those findings which are believed to be common to both diabetic retinopathy and vascular hypertension, especially in elderly patients, were carefully recorded as were the findings which by common consent are alleged to indicate diabetes.

The fundi were classified in three groups:

- (1) **Minimal Diabetic Retinopathy.**—Few haemorrhages and few small areas of exudate, with:
 - (a) Minimal hypertensive vascular changes;
 - (b) Moderate hypertensive vascular changes;
 - (c) Maximum hypertensive vascular changes.
- (2) **Moderate Diabetic Retinopathy.**—More marked exudates, haemorrhage, and small central capillary aneurysms, with:
 - (a) Minimal hypertensive vascular changes;
 - (b) Moderate hypertensive vascular changes;
 - (c) Maximum hypertensive vascular changes.
- (3) **Marked Diabetic Retinopathy.**—Severe haemorrhages and exudates (retinitis proliferans), with:
 - (a) Minimal hypertensive vascular changes;
 - (b) Moderate hypertensive vascular changes;
 - (c) Maximum hypertensive vascular changes.

The presence, or absence of any of the ocular complications associated with diabetes was noted. The systolic and diastolic pressure were measured and the age of the patient recorded. Blood sugar readings were taken and the presence or absence of glycosuria or acetonuria ascertained.

At the conclusion of these clinical recordings and before the administration of cyancobalamin, a selected number of patients had each fundus photographed in colour.

Test Cases.—Cyancobalamin was given intramuscularly daily for 14 days in doses of 1,000 μ g. to ten selected patients. At the end of the course of treatment a further, similar clinical examination of each fundus was made, the details were recorded, and a second photograph in colour was taken. A third clinical examination was made up to 6 months after treatment. The particulars in the ten test cases are recorded in Table I (opposite).

Case Reports

Case 1, a male aged 44 years.—Diabetes discovered on routine examination in 1944.
Morning blood sugar 120 mg.
Blood pressure 140/90, stones in kidney.
Treatment by diet and insulin, soluble and clear.
Visual acuity 6/9 in each eye.

Fundus Examination.—Before treatment, Group 2a; after treatment, comparison of the coloured photographs showed in this particular case a marked lessening of the exudate on the temporal side (Figs 1 and 2, opposite). The haemorrhages appeared little changed. Examination of the fundi ophthalmoscopically showed similar improvement even 6 months after treatment.

TABLE I

TEN CASES OF CONTROLLED DIABETES TREATED WITH CYANCOBALAMIN

Case No.	Sex	Age (yrs)	Duration of Diabetes (yrs)	Blood Sugar (mg.)	Blood Pressure (mm. Hg)	Corrected Visual Acuity			
						Before Treatment		After Treatment	
						Right	Left	Right	Left
1	M	44	13	120	140/90	6/9	6/9	6/9	6/6
2	F	56	26	240	150/80	<6/60	<6/60	<6/60	<6/60
3	F	36	23	130	120/70	<6/60	1/60	<6/60	6/60
4	M	56	17	180 to 240	140/80	6/9	6/9	6/5	6/5
5	F	61	5	280 to 384	140/80	6/60	6/18	6/36	6/36
6	F	22	10	210	130/90	6/12	6/9	6/12	6/9
7	M	37	17	170 to 250	130/90	6/9	6/9	6/5	6/5
8	F	65	2	290	210/90	3/60	2/60	3/60	2/60
9	F	68	3	320	230/160	6/6	6/6	6/6	6/6
10	F	49	9	130	170/90	6/24	Counting fingers at 2 ft	6/24	6/60

FIG. 1.—Case 1, before treatment.

FIG. 2.—Case 1, after treatment.

Case 2, a female aged 56 years.—Diabetes discovered after the loss of a child 26 years previously.

Blood sugar 240 mg.

Blood pressure 150/80, blood urea 140 mg. per ml.

Treatment by diet and insulin.

Visual acuity < 6/60 in each eye.

Fundus Examination.—Before treatment, Group 3c; after treatment, very little change was noticed in the right eye, the degree of retinitis proliferans had increased in the left.

Case 3, a female aged 36 years.—Diabetes disclosed in 1934 by boils on the legs.

Blood sugar 130 mg.

Blood pressure 120/70.

Treatment by insulin.

Visual acuity < 6/60 in the right eye with cataract and 1/60 in the left.

Fundus Examination.—Before treatment, Group 3a; after treatment, condition unchanged.

Case 4, a male aged 56 years.—Diabetes discovered in 1940 on insurance examination.

Blood sugar 180 to 240 mg.

Blood pressure 140/80.

Treatment by diet and insulin lente.

Visual acuity 6/9 in each eye.

Fundus Examination.—Before treatment, Group 2b; after treatment, examination of the fundi photographs showed a lessening in the amount of retinal exudate in the central area. This lessening was more marked in the right eye than in the left. No other changes were noted. Clinical examination 6 months later showed this improvement to be maintained.

Case 5, a female aged 61 years.—Diabetes disclosed on the patient's complaint of loss of weight in 1952.

Blood sugar 280 to 384 mg.

Blood pressure 140/80.

Treatment by diet and insulin.

Visual acuity 6/60 in the right eye and 6/18 in the left.

Fundus Examination.—Before treatment, Group 3b; after treatment, both eyes showed haemorrhage and hard exudate, a typical text-book picture of diabetic retinopathy.

Case 6, a female aged 22 years.—Diabetes discovered 1947 at age of 12 years because of the patient's excessive thirst.

Blood sugar 210 mg.

Blood pressure 130/90.

Treatment by diet and insulin.

Visual acuity 6/12 in the right eye and 6/9 in the left, which showed early peripheral lens sclerosis.

Fundus Examination.—Before treatment, Group 2a; after treatment, the fundi seemed of better colour, but there appeared to be a few more haemorrhages on ophthalmoscopic examination. The exudates were unchanged.

Case 7, a male aged 37 years.—Diabetes discovered in 1940 at the time of an appendicectomy.

Blood sugar 170 to 250 mg.

Blood pressure 130/90.

Treatment by diet and insulin lente.

Visual acuity 6/9 in each eye.

Fundus Examination.—Before treatment, Group 3a; after treatment, clinically the right fundus seemed "drier", and the density and degree of exudate around the macula seemed less. The left eye showed very little change.

Case 8, a female aged 65 years.—Diabetes disclosed in 1955 by refractive changes.
Blood sugar 290 mg. Blood pressure 210/90.
Treatment by diet and insulin.
Visual acuity 3/60 in the right eye and 2/60 in the left; there were right lens changes.
Fundus Examination.—Before treatment, Group 1c; after treatment, unchanged.

Case 9, a female aged 68 years.—Diabetes disclosed in 1954 when the patient complained of pain in the legs and thirst.
Blood sugar 320 mg. Blood pressure 230/160.
Treatment by diet.
Visual acuity 6/6 in each eye.
Fundus Examination.—Before treatment, Group 2b; after treatment, unchanged.

Case 10, a female aged 49 years.—Diabetes disclosed in 1948 when the patient complained of loss of weight and skin irritation.
Blood sugar 130 mg.
Blood pressure 170/90. Neuropathy present.
Treatment by diet and insulin.
Visual acuity 6/24 in the right eye and counting fingers at 2 feet in the left.
Fundus Examination.—Before treatment, Group 3a; after treatment, more haemorrhages were visible below, but the degree of exudate was less on ophthalmoscopic examination though this was not seen in the photograph.

Controls.—A similar number of controls was selected and similarly examined (Table II). No vitamin B₁₂ was administered and after a lapse of 6 months the cases were re-examined and the findings compared. Although many of the controls, judged by the blood sugar, appear to be severe diabetics, the Table shows that they were not necessarily severe cases of diabetic retinopathy.

TABLE II
TEN CONTROL SUBJECTS

Case No.	Sex	Age (yrs)	Duration of Diabetes (yrs)	Blood Sugar (mg.)	Blood Pressure (mm. Hg)	Corrected Visual Acuity Initial Reading		Fundus Group	Corrected Visual Acuity Final Reading	
						Right	Left		Right	Left
1	F	65	53	270	170/100	Hand movements	6/36	2b	Hand movements	6/60
2	F	24	1	290	120/90	6/24	6/18	1a	6/24	6/18
3	F	64	1	225	240/110	< 6/60	6/60	2c	< 6/60	Venous thrombosis
4	M	56	10	220	160/90	6/12	6/36	1a	6/9	6/24
5	F	65	3	180	250/120	< 6/60	6/36	3b	6/60	6/36
6	F	57	5	190	145/95	6/18	< 6/60	2a	6/18	6/60
7	F	28	2	150	130/100	6/24	6/24	2a	6/24	6/24
8	M	49	4	190	150/95	6/9	Perception of light	2a	6/9	Perception of light
9	F	63	9	200	190/110	6/24	Hand movements	2b	6/24	Hand movements
10	M	30	8	190	130/90	6/24 partly	6/60	2a	6/24	6/60

Results

The results of the investigation, while not impressive, showed that in Cases 1, 4, and 7 the degree of exudate in the retina was less after treatment than before as judged by both ophthalmoscopic examination and by fundus photography (Table III).

TABLE III
COMPARISON OF CLINICAL FINDINGS (CONTROLS)

Case No.	Initial Examination		Final Examination	
	Right Eye	Left Eye	Right Eye	Left Eye
1	Exudates, haemorrhages	Exudates, haemorrhages, synechiae	Unchanged	Unchanged
2	Fundus clear	Hard exudates on temporal side	One or two tiny round haemorrhages, few pin-points of exudate on temporal side	Unchanged
3	Senile lens changes, flame-shaped and round haemorrhages, one or two aneurysms and areas of exudate	Senile lens changes, many flame-shaped haemorrhages, exudate	Unchanged	Venous thrombosis
4	Hard exudates in paramacular area	Exudates in central area	Micro-aneurysms below the disc	Unchanged
5	Masses of hard exudate in central area, small round haemorrhages throughout, senile lens changes	Hypertensive retinopathy	Unchanged	Unchanged
6	Lens spikes, hard exudates in centre of fundus, few haemorrhages	Masses of exudates below the macula	Increase of exudate and haemorrhages	Increase of exudate, haemorrhages present
7	Exudates and haemorrhages scattered throughout	Central exudate and haemorrhages	Unchanged	Unchanged
8	Nasal side of disc showed tiny aneurysms, about eight in number, "bunch of grapes" formation	Central choroidal sclerosis, aneurysm below macular area	Unchanged	Unchanged
9	Aphakia Haemorrhages and exudates in macular area	Cataract	Unchanged	Unchanged
10	Small haemorrhages and exudate in centre of fundus	Early peripheral lens changes, one or two tiny round haemorrhages in centre	Unchanged	Retinal oedema

No similar lessening of exudate was noticed in any of the controls. This improvement has maintained for up to 6 months in some cases. While it is agreed that the exudates in any form of exudative retinitis tend to lessen, particularly after the "peak period" of the condition is passed, it is perhaps a little significant that in one or two cases in the series this took place within a definite period and under similar conditions.

Lederer, Brichant, and Brichant-Doyen (1955) were of the opinion that the administration of vitamin B₁₂ to diabetics with retinopathy increased the capillary resistance. No significant lessening of superficial or deep haemorrhages was noted in the majority of cases of this series.

Summary

Ten cases of diabetic retinopathy were ophthalmoscopically examined before and after a course of treatment with intramuscular cyanocobalamin (vitamin B₁₂) in doses of 1,000 µg. daily for 14 days. Selected cases had coloured fundus photographs taken before and after treatment. An equal number of controls was similarly examined and reported upon.

It was noted on comparing the photographs before and after treatment that in three cases the degree of retinal exudate had diminished.

Of the ten cases clinically examined five had improved; of this number two cases were in Group 2a, which was considered the most important, one in Group 2b, and two in Group 3a.

Of the controls the condition in five cases was unchanged except for variations in visual acuity. In all the remaining five the condition had deteriorated in one or other eye.

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