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EVALUATION OF AN ANDROGEN, METHYLANDROSTENEDIOL, IN THE TREATMENT OF DIABETIC RETINOPATHY*

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DIABETIC retinopathy is often a serious visual disabling complication of long-standing diabetes mellitus, although unless combined with nephropathy and hypertension the prognosis as to life is not poor. Little is known of its pathogenesis and no specific therapy is so far available. Proper control of the diabetes with insulin and a carbohydrate restricted diet remain the only feasible means of prophylaxis.

The claim of Saskin, Waldman, and Pelner (1951) that intramuscular administration of testosterone resulted in unequivocal improvement in more than one-third and definite improvement in an additional 40 per cent. of patients with retinopathy was therefore of interest. According to Bedrossian and others (1953), who could not substantiate Saskin's observations, testosterone had been considered effective because of a favourable influence on abnormal liver function and protein metabolism, factors which may produce diabetic complications. Pelner and Waldman (1954) subsequently suggested that the therapeutic effect of testosterone is to antagonize the action of corticotrophin, the increased endogenous secretion of which may also be implicated in the pathogenesis of retinopathy. Bedrossian and others (1953) concluded that testosterone therapy given intramuscularly for periods of 5 months failed to benefit diabetic retinopathy to a greater extent than control injections of saline.

Present Investigations

Patients were selected because they had retinopathy of such a degree that improvement might be expected if this form of treatment were indeed effective.

The patients' ages ranged from 18 to 58 years and the duration of the diabetes varied from 2½ to 22 years (average 12·8). The high proportion of women (18 women to 9 men) is probably due to the greater number of women attending the clinic rather than to any genuine sex distribution of retinopathy.

A total of 27 patients received an androgen, methylandrostenediol, by mouth in doses of from 60 to 200 mg. a day for between 3 and 6 months (average 16·2 weeks). This particular preparation was chosen because it can be given orally and, according to Henderson and Weinberg (1951) and Kasdon and others (1952), has a less potent masculinizing effect than testosterone.

A sub-group of ten of these patients with blood pressures above 180/110 mm. Hg were given both methylandrostenediol and a ganglion-blocking agent—subcutaneous hexamethonium bromide in three cases, and oral pentapyrrolidinium bitartrate (Ansolysen) in seven. In addition, a control group of ten hypertensive

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diabetics received Ansolysen alone. The majority of these hypertensive patients, thirteen out of twenty, appeared to be suffering from essential hypertension rather than from diabetic glomerulo-sclerosis. The degree of retinopathy did not appear to be related to the severity of the diabetes, eight (22·9 per cent.) cases being adequately controlled by dieting without insulin.

The severity of the retinopathy was graded as follows:

Stage I. Capillary micro-aneurysms or mild phlebo-sclerosis.
Stage II. Micro-aneurysms, punctate and " wet sponge " haemorrhages, and only a small amount of exudate.
Stage III. As above, but with more advanced haemorrhages and exudate.
Stage IV. Severe retinopathy with pre-retinal or vitreous haemorrhages.
Stage V. Retinitis proliferans of the fibrous or vascular types, or retinal detachment.

Such a classification is imprecise, but allows a reasonable degree of clinical assessment, and the distribution of cases according to treatment groups. Grading, depending on the poorer eye, is shown in Table I.

TABLE I

TYPE OF THERAPY RELATED TO GRADE OF RETINOPATHY

Treatment	Grade of Retinopathy					Total No. of Patients
	I	II	III	IV	V	
1. Methylandrostenediol alone	3	4	5	3	2	17
2. Methylandrostenediol and ganglion-blocking agent	1	2	3	3	1	10
3. Ganglion-blocking agent alone	2	2	3	2	0	9

Results

The ophthalmoscopic picture in diabetic retinopathy is by no means static and improvement may occur spontaneously, although the general trend is one of steady degeneration, in most cases over a period of years. Micro-aneurysms, phlebo-sclerosis, and hard exudates are unlikely to resolve, but haemorrhages of the " wet sponge " or pre-retinal type can often be observed to clear in one situation whilst similar lesions develop elsewhere.

It is important that this natural variation should not be attributed to any therapy in current use. The co-existence of hypertensive retinopathy may further complicate matters. By the time true retinitis proliferans has developed, little spontaneous improvement can be expected and no form of treatment is likely to be of value.

In none of these 27 cases was the degree of improvement greater than might be expected to occur without treatment (Table II, opposite).

Of the three who are listed as improved, one had a vascular type of retinitis proliferans of sudden onset with a bizarre pre-retinal " haze " and improvement was slight. The other two were treated with both androgen and hexamethonium but the improvement in hypertensive retinopathy made assessment difficult. A combination of these drugs did not seem more

TABLE II

RESPONSE TO THERAPY

Treatment	Total No. of Patients	Result		
		Improved	Unchanged	Worse
1. Methylandrostenediol alone	17	1	13	3
2. Methylandrostenediol and ganglion-blocking agent	10	2	6	2
3. Ganglion-blocking agent alone	10	1	8	1

effective than either alone and three patients had recurrences of vitreous haemorrhages whilst under treatment.

It must be admitted that only ten of the twenty hypertensives showed a significant fall in diastolic blood pressure of over 20 mm. Hg or postural hypotension whilst taking ganglion-blocking agents.

Conclusion

No evidence has been obtained that methylandrostenediol given by mouth in doses of up to 200 mg. a day exerts any beneficial influence on diabetic retinopathy when given for periods of between 3 and 6 months. No untoward side-effects developed in the women and no appreciable alteration, such as the improvement reported by Klotz and Avril (1952), was noted in the diabetic state. Our results agree with those of Bedrossian and others (1953), and except in cases with definite evidence of hypertensive neuroretinopathy the addition of a ganglion-blocking agent failed to potentiate the action of the drug. It is of interest that three patients were treated with a mixed injection of soluble insulin and hexamethonium bromide in the same syringe without obvious impairment of insulin activity. Such a combined treatment appears useful in the treatment of hypertensive diabetics, particularly those with advanced diabetic nephropathy. In four patients in whom serum-polysaccharides were estimated there was no significant change before or after treatment with methylandrostenediol. From preliminary studies it also seems unlikely that the combined use of cyanocobalamin (vitamin B_{12}) and androgens is any more effective.

Summary

(1) 27 patients with diabetic retinopathy of varying degrees of severity were treated with methylandrostenediol. No significant improvement was noted after periods of treatment averaging 16·2 weeks.

(2) Ten of these patients, and a control group, were also given ganglion-blocking agents because of hypertension. In neither group was there any improvement in the diabetic picture, although hypertensive retinopathy appeared to benefit.

(3) Proper control of diabetes by carbohydrate restricted diet and insulin remains the most practical means of prophylactic treatment.

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