CONDITIONED CORNEAL VASCULARITY IN RIBOFLAVIN DEFICIENCY

Report of a Case

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IN 1940 Sydenstricker and his associates [1] published their observations on corneal vascularization in man, which was similar to that described previously by Bessey and Wolbach [2] in rats maintained on riboflavin-deficient diet. Since then a large number of papers on the subject have appeared, and the first enthusiastic response of confirmation soon made way to criticism and doubt; the latter trend, as happens frequently, shifted the general opinion far in the opposite direction, causing a number of workers to deny the existence of corneal vascularity as a result of ariboflavinosis in man. This negative attitude seems to have taken root to a certain extent in the collective mind of ophthalmologists.

Corneal vascularity caused by riboflavin deficiency is a clinical entity. It is probably true that it cannot be diagnosed by its morphologic aspect alone, although the appearance of regular, fine capillaries in the entire circumference of the cornea, which leave the limbic zone and pass centripetally into the clear cornea, is highly suggestive; if, in addition, three conditions are fulfilled—inadequate riboflavin intake, low riboflavin level of the blood or urine and response to treatment with riboflavin—there is no doubt as to the cause of the lesion.

The following case report is presented because any additional clinical observation on the relation of this lesion to riboflavin deficiency is worthy of attention if it establishes the validity of the concept first expressed by Bessey and Wolbach and by Sydenstricker and associates.

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1. Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M., and Kruse, H. D.: Ocular Manifestations of Ariboflavinosis: Progress Note, J. A. M. A. **114**:2437 (June 22) 1940.

2. Bessey, O. A., and Wolbach, S. B.: J. Exper. Med. **69**:1, 1939.

REPORT OF CASE

E. A., a Greek veteran aged 38, was sent to this country by his government to seek cure for blindness, which he had contracted during army service. It was hoped that a corneal transplant might benefit him, and he came to the Special Eye Bank Clinic (Manhattan Eye, Ear and Throat Hospital), where Dr. R. Townley Paton referred him to the Nutrition Clinic of the Department of Health of the City of New York for study.

His vision had always been adequate prior to a shell blast injury received to his face and eyes in the early stages of the Greek-Italian war (1940). At this time he was taken prisoner by the Italians, and he spent the next five years in Italian and German prison camps. During this time his eyesight deteriorated steadily, and when he was finally returned to his country he was blind for all practical purposes.

When he was first seen at the Nutrition Clinic, he was a thin, dejected-looking man, who was hardly able to find his way in unfamiliar surroundings. His vision

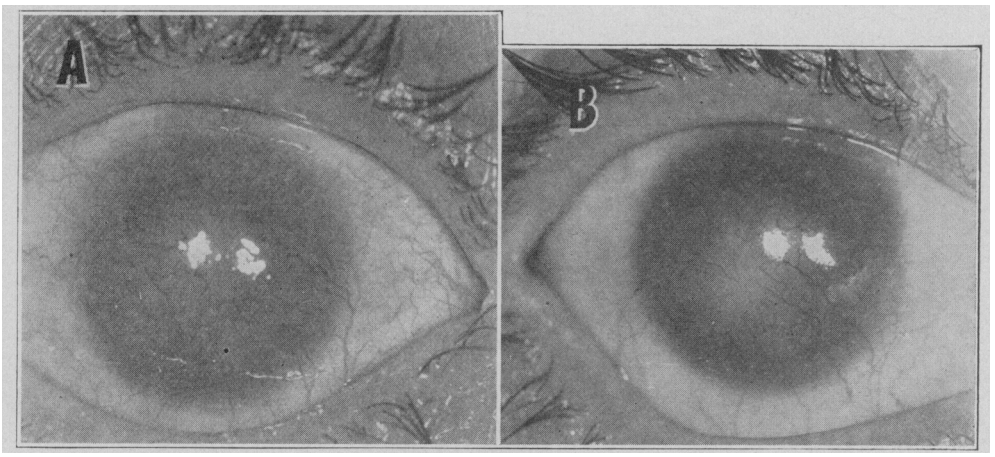

Fig. 1.—Eyes before riboflavin therapy was started. *A*, right eye. *B*, left eye. Note the irregularity of the normally circular light reflex on the cornea, indicating the degree of unevenness of the epithelium.

was reduced to counting fingers at 2 feet (60 cm.). Both eyes showed injected conjunctivas, and photophobia was present. Both corneas showed diffuse opacities over the entire surface, chiefly in the superficial layers and the epithelium, with numerous engorged blood vessels entering the cornea from every point of the periphery, traversing it and freely communicating with each other. On the posterior surface of each cornea and the anterior surface of the lens, fine and gross particles of iris pigment could be discerned (fig. 1 *A* and *B*). There was dyssebacia of the face, but no glossitis or cheilosis.

A reconstruction of his diet during the war years showed that he had been on a diet seriously deficient in all members of the vitamin B complex, as well as in other vitamins. Riboflavin must have been practically absent from his diet. During all these years he had formed a faulty dietary pattern, and even now, with all restrictions removed, he consumed a diet inadequate in riboflavin. Examination of the urine for riboflavin at the Nutrition Clinic showed 70 micrograms in a four hour fasting specimen of 340 cc., a value indicating a low riboflavin intake.

Treatment was instituted with administration of 15 mg. of riboflavin by mouth. After one week, regression of the hyperemia of the corneal vessels could be observed, and the cutaneous lesion on the face was clearing. By the end of the third week the vessels in the cornea were considerably less noticeable. Some of the smaller ones could not be seen at all with the slit lamp, and the larger ones were less engorged and showed a reduction in caliber. Vision had improved to counting of fingers at 6 feet (180 cm.). The patient had gained 3 pounds (1.3 Kg.) and felt much better generally.

At the end of seven weeks, with no additional therapy, the majority of the vessels in the cornea had become invisible. Here and there, blood corpuscles could be seen in collapsed capillaries. In other capillaries very sluggish circulation was still evident. The opacities had receded considerably, and the patient counted fingers at 10 feet, or 3 meters (fig. 2). (He was myopic, and the visual acuity could still be improved with glasses.)

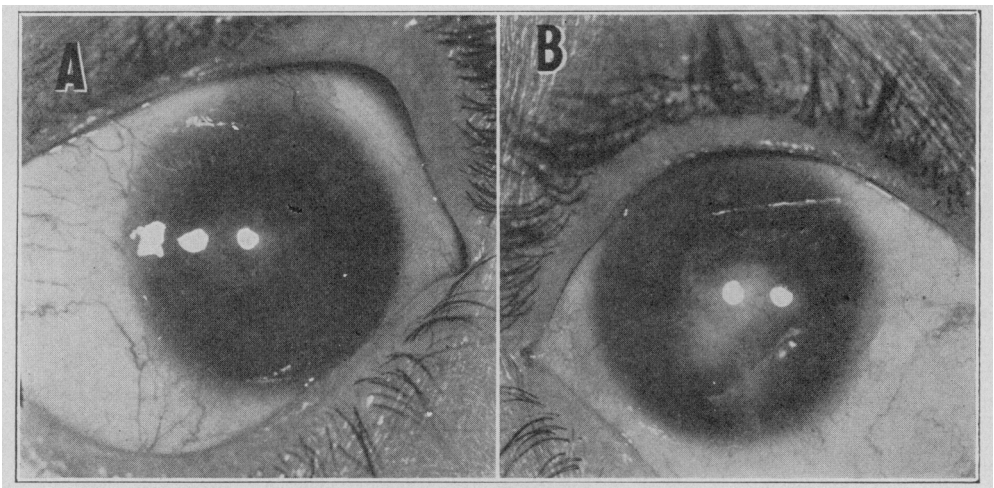

Fig. 2.—Eyes seven weeks later. *A*, right eye. *B*, left eye. Note that the light reflexes on the cornea are nearly circular, indicating that the epithelium is now almost normal.

There does not seem to be any reason to doubt that this case was one of true riboflavin deficiency. All the conditions are fulfilled: low riboflavin intake over a long period, low riboflavin level of the urine and prompt response to riboflavin therapy. Although a deficiency of all vitamins was probably present, only riboflavin was given as a therapeutic trial. It is hardly conceivable that pathologic changes of the degree described would recede spontaneously after having been present so many years. It can be concluded, then, that a long-standing deficiency of riboflavin in this patient's diet resulted in the specific lesions in his eyes, which were influenced most favorably by specific therapy.

This explanation, nevertheless, is not fully satisfactory. There must have been a very great number of people under nutritional handicaps similar to those of this patient during the war and the postwar years.

Yet, during the last few years, thousands of prisoners of war and inmates of concentration camps have been seen by a number of investigators, without any published reports indicating the presence of corneal vascularity in the degree seen in the present case. It appears, then, that the nutritional factor is not the sole explanation of the corneal vascularity in this case. An additional factor must have been present which, in combination with riboflavin deficiency, produced the clinical picture.

It has been shown by Bessey and Lowry [3] that the riboflavin concentration in the cornea of the rat must fall to less than 50 per cent of the normal before signs of corneal vascularity appear. Clinical investigations now under way seem to indicate that chronic riboflavin deficiency may produce corneal vascularization only if and when the cornea is exposed to a traumatic factor—be it accidental injury, surgical intervention, chronic mechanical or solar irritation or an allergic reaction. Landau and I [4] have argued the case for the last contingency in the instance of eczematous keratitis. The present case seems to support a position of major importance for trauma. During his army service the patient was subjected to bomb and shell blast on several occasions, and on one of these he received the full blast of an exploding shell in his face. The iris pigment scattered over the surfaces of the anterior chamber in both eyes was probably a result of this blunt injury. It seems justifiable to assume that the cornea was injured superficially and that the healing process was disturbed by the presence of a serious riboflavin deficiency.

Riboflavin is a prosthetic group of the yellow respiratory enzyme. Bessey and Wolbach [2] postulated that in its absence the disturbance of the respiratory processes in the avascular cornea is relieved by ingrowing vessels. Contrary to earlier opinions, the metabolism of the corneal epithelium is very active (Lowry and Bessey,[5] Robbie and associates [6]). An injured cornea requires more oxygen, consequently more respiratory enzyme, and therefore more riboflavin, than a healthy one. A degree of riboflavin deficiency which will remain subclinical under normal conditions will lead to corneal vascularization to relieve the respiratory deficit when pathologic conditions raise the corneal metabolism. It has been shown by Lowry and Bessey [5] that a prolonged deprivation of riboflavin leads to a fall in the riboflavin concentration in the cornea, causing a definite handicap to the healing of experimental lesions.

The corneal condition in the case presented here had remained static for many months. The patient had received the usual local treatment

3. Bessey, O. A., and Lowry, O. H.: J. Biol. Chem. **155**:635, 1944.

4. Stern, H. J., and Landau, J.: Am. J. Ophth. **31**:1619 (Dec.) 1948.

5. Lowry, O. H., and Bessey, O. A.: J. Nutrition **30**:285, 1945.

6. Robbie, W. A.; Leinfelder, P. J., and Duane, T. D.: Cyanide Inhibition of Corneal Respiration, Am. J. Ophth. **30**:1381 (Nov.) 1947.

and had failed to show any response. The improvement under riboflavin therapy was too dramatic to be explained by anything but the contention offered here. It can safely be assumed that in this case a chronic deficiency of riboflavin had been "conditioned" (Jolliffe [7]) by superficial injuries to the cornea, the nutritional factor complicating their healing and causing the extensive opacities and vascularity which rendered him nearly blind. Specific therapy with the missing vitamin relieved this condition to such a degree that the patient acquired useful vision within a few weeks, thus obviating the necessity of corneal transplantation.

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7. Jolliffe, N.: Conditioned Malnutrition, J. A. M. A. **122**:299 (May 29) 1943.