correction in the other cities in this low mortality group (the first ten), temperature in this case being a factor of minor importance."

This subject was further considered by Dr. L. A. Pequegnat, Deputy Medical Officer of Health, Toronto, who presented a paper entitled "The Present Problem in Infant Mortality" to the Academy of Medicine, Toronto. The paper was published in the *Canadian Public Health Journal* (1938, 29, 477). It reproduces a table of Bellows and Reed's. In this paper the rates for Toronto and Vancouver are presented for the years 1930 to 1935. In 1930 and 1935 the infant mortality rate in Toronto was double the Vancouver rate. It would seem, therefore, that the lower rates of Vancouver and Victoria require in their consideration some of the factors studied by Bellows and Reed. That climate alone is not the factor is evidenced by the fact that the rate in Calgary in 1940 was 31.2 and in Edmonton 30.6, in comparison with 25.6 in Vancouver and 28.4 in Victoria. Figures for other cities in Canada are: St. John, N.B. (65% of milk pasteurized), infant mortality rate 55 (1940); Montreal (95% pasteurized), rate 70 (1939) and 58 (1940); Three Rivers, Que. (60% pasteurized), rate 97 (1940). In Ontario all municipal milk supplies were required to be pasteurized in 1938. Data for 1940 give the following infant mortality rates: Hamilton 33, London 36, Kitchener 37, Ottawa 49.

From these rates it is evident that neither climate nor pasteurization of milk gives an answer to the differences in rates. The larger number of deaths due to prematurity, etc., is an important factor.

THE OCULAR CRITERIA OF DEFICIENCY OF RIBOFLAVIN

BY

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Since Bessey and Wolbach (1939) showed that corneal vascularization was a sign of riboflavin deficiency in rats, and since the publication of two papers on ocular manifestations of ariboflavinosis, by Kruse *et al.* (1940) and Sydenstricker *et al.* (1940), there has been a spate of enthusiastic but uncritical investigations. It is therefore necessary that there should be some attempt to clarify the confusion of thought and to correct the looseness of terminology that has arisen. Evidence of this confusion is to be found, for example, in a recent report of an investigation by Scarborough (1942) in which he has taken the sign of circumcorneal injection as being of primary importance. This sign can occur in early ariboflavinosis, but it certainly is not pathognomonic; and I do not find anything in the paper by Sydenstricker *et al.* (1940), which is quoted by Scarborough, to indicate that this isolated sign should be so interpreted. A further discrepancy which I have noted occurs in the two papers mentioned above, which in one place describe the earliest change noted as being a superficial invasion of the cornea by capillaries, and in another place say that "the earliest and most common sign of ariboflavinosis is circumcorneal injection." Also the terms "circumcorneal injection" and "ciliary congestion" are used indiscriminately without indicating whether just some degree of fullness of the superficial pericorneal vessels is meant or whether there is an intense ciliary blush. From my own recent observations and from verbal corroboration by other observers I question whether what is clinically known to ophthalmologists as circumcorneal injection is necessarily an accompaniment of mild early corneal vascularization as we see it in this country.

As the ocular changes in early deficiency of riboflavin are concerned with the vascular supply of the limbus it is essential that observers first should have an exact knowledge of the normal blood supply and arrangement of vessels at the limbus;

secondly, they should have an accurate idea of the changes which, in the light of our present knowledge, may be expected to occur; and, thirdly, they should know what other conditions may produce somewhat similar appearances and how these may be distinguished. I propose to give a brief outline of these three points.

Fortunately it is rare at present for nutritional deficiencies to be more than slight in this country, and therefore, as it is the mild rather than the gross changes that are being considered, the picture that we may expect to find will scarcely be comparable with the fully developed cases described by Sydenstricker *et al.* (1940) and Kruse *et al.* (1940). I am not considering such signs as pigment deposits on the iris and mydriasis, as the significance of these has not yet been adequately established.

The Normal Blood Supply of the Limbus

The blood supply of the pericorneal region comes from the anterior ciliary arteries arising indirectly from the ophthalmic arteries via the arteries of the four recti muscles, each tendon being accompanied by two, except the external rectus, which has only one. These arteries pass forward on the episclera, giving branches to the sclera, corneal margin, and conjunctiva. The main branch of each artery pierces the sclera about 4 mm. from the corneal margin to enter the ciliary muscles, where it anastomoses with the long posterior ciliaries to form the *circulus iridis major*. Before piercing the sclera the anterior ciliary arteries give off the anterior conjunctival branches, which run forward deep to the posterior conjunctival arteries and anastomose to form the pericorneal plexus, consisting of a series of arcades parallel with the corneal margin. These give off final branches, marginal loops which bend round on their tracks to form venules leading into a venous plexus built up on similar lines. The anterior conjunctival arteries also give off small posterior branches to anastomose with the posterior conjunctival arteries, which come from the palpebral branches of the nasal and lacrimal arteries of the lids.

The pericorneal plexus is in two layers—the superficial conjunctival and the deep episcleral. This distinction is important because in superficial affections of the cornea the superficial portion is injected and may rightly be termed circumcorneal injection, whereas in diseases of the iris, ciliary body, or deep part of the cornea the deep episcleral portion becomes congested and gives rise to the rose-pink or violet band typical of ciliary congestion. This deep ciliary congestion is always a serious sign as indicative of uveal disease, but superficial circumcorneal injection can be transiently produced by vigorously rubbing the eye for a moment; and it results from irritations such as exposure to wind, cold, bright light, mild chemical irritants, mild infection, and numerous other causes. From such causes there must be a considerable proportion of the population showing circumcorneal injection, which would fit the description given in the paper by Sydenstricker *et al.* (1940) as "often it was grossly visible, frequently it could be seen with a hand lens or ophthalmoscope, and always it was obvious on slit-lamp inspection as marked congestion and proliferation of the limbic plexus." On this point I would ask what evidence there is that there is any real proliferation and not only engorgement of pre-existing but empty and therefore invisible vessels.

The extent to which the vessels may, within normal limits, extend on to the cornea should also be defined. The limbus is the whole zone in which the sclera and cornea overlap owing to the edge of the cornea being inset like a watchglass in a groove in the sclera. Though it is said to be 1 mm. in width, it is very variable, often being much wider than this. With the slit-lamp the whole width of the limbus appears like ground glass, increasing in opacity peripherally. It may be segmented by digitations or may appear homogeneous. The marginal plexus is described as occupying a triangular area whose apex lies where Bowman's membrane ends and whose base is formed by episcleral and scleral tissue (Wolff, 1940). Thus it is normal for vessels to occupy the whole width of the limbus, and there is not necessarily an avascular zone between the plexus and sclero-corneal junction; and capillaries which do not extend beyond the limbus thus defined are considered to be within the limits of normal.

Ocular Appearances in Riboflavin Deficiency

The chief sign is a superficial invasion of the cornea by very fine capillaries arising from the apices of the marginal loops. These lie just deep to the epithelium and extend evenly as streamer-like vessels which anastomose to form a series of loops from the apices of which more capillaries grow towards the centre, giving the appearance, with the slit-lamp, of fine almost parallel vessels extending on to the cornea round the whole of its periphery in both eyes. The extent of invasion may differ in each eye. Superficial and interstitial opacities develop at various stages, but are definitely later in occurrence than the initial vascularization. In more advanced cases the vessels penetrate to a greater depth into the substantia propria. In a proportion of cases there is some injection of the pericorneal plexus, which in mild deficiency is confined to the superficial conjunctival layer.

Other Causes of Corneal Vascularization

The cause of the most extensive vascularization of the cornea is interstitial keratitis, in which the new vessels invading the cornea come from the anterior ciliary arteries as they pass deeply through the sclera, and thus, as the sclera is opaque, they disappear behind the limbus. With the slit-lamp they are seen to lie in the posterior half of the substantia propria over the whole area of the cornea and are irregular in arrangement, in contradistinction to the superficial centripetal regular arrangement of capillaries in riboflavin deficiency.

Some other conditions in which vascularization of the cornea may occur are vitamin A deficiency, tryptophan deficiency, injury of corneal epithelium due to chemical irritants, diseases causing pannus, such as trachoma, phlyctenular keratitis, pannus degenerativus, and also any superficial keratitis.

Bessey and Wolbach (1939) describe corneal vascularization, similar to that due to lack of riboflavin, in rats deficient in vitamin A; but this is not usually described as a sign associated with keratomalacia in human subjects, nor have I found it as an early sign in people known to be deficient in vitamin A. Albanese and Buschke (1942) describe vascularization of the cornea similar to ariboflavinosis in cases of tryptophan deficiency in both adult and growing rats and reversible by giving tryptophan. It is unlikely, however, that this specific deficiency will arise without other evidence of deficiency of protein. Vascularization from chemical causes is not usually bilateral nor so regular and uniform, except in the case of exposure to chemical vapour, which can give a comparable picture; but the history and the somewhat atypical appearance should enable it to be differentiated.

The vascularization of trachomatous pannus is confined to the upper part of the cornea under the upper lid and, as is characteristic of all pannus formation, there is infiltration of granulation tissue and leucocytes between and around the vessels. Phlyctenular pannus may occur right round the periphery, but it is of the pannus type of vascularization with coarser vessels, and can be further distinguished by symptoms of laceration, photophobia, irritation, and blepharospasm, which are extreme in this condition. Pannus degenerativus occurs in old blind eyes and starts in the substantia propria.

Out of 1,059 presumably normal people whom I recently examined in search of signs of riboflavin deficiency 31 (3%) showed corneal vascularization compatible with ariboflavinosis, and of these only 14 were recorded as having any injection or even fullness of the limbic plexus. Among these 31 only 5 complained of any subjective symptoms such as burning, irritation, or laceration, and none volunteered a history of twilight blindness, which Pock-Steen (1939) asserts is an early sign. In only 4 cases was the visual acuity in both eyes less than 6/6. Eight cases showed other signs of riboflavin deficiency such as glossitis or cheilosis. In all these subjects a full clinical examination was carried out and their night vision was tested. These results will be published at a later date.

I would suggest that, as in the cases examined by Scarborough (1942) the greatest incidence of pericorneal injection occurred in the age group 50-59, this may be a normal finding, since people of this age rarely have the clear white limbus normally found in youth.

Since the 47 patients in Sydenstricker's investigation were being given 300 mg. of nicotinic acid daily it appeared possible that the vasodilator action of this drug might have some influence on the high incidence of circumcorneal injection found. In order to test the possibility of this, I examined the eyes of 6 normal medical students and then administered 200 mg. of nicotinic acid by mouth. When examined 20 to 30 minutes later two showed marked injection of perilimbal plexus, three a moderate degree of injection, and one very little change. These subjects continued to take 200 mg. daily for five days, and were finally examined again 8 hours after taking the last dose. Three showed no increased vasodilatation compared with their original state and three showed a very slight but not significant increase. A further series of 6 subjects were given 200 mg. of nicotinic acid after examination, and then examined at half-hourly intervals. One showed marked, three moderate, and two only slight injection. The two slight and one moderate had returned to normal in 1½ hours, and two moderate and one marked case had returned to normal in 2 hours. Thus it is inferred that the local effect of these doses of nicotinic acid is important only within 2 hours of its administration.

It may be said that I have committed the error that I have criticized in Scarborough's paper in laying the emphasis on one isolated symptom—viz., corneal vascularization. This at least is more justifiable in that it is generally recognized as a more characteristic sign, and, according to Bessey and Wolbach (1939), "it precedes all other demonstrable lesions of the deficiency." Even so, I should refrain from diagnosing a definite deficiency on this single finding in the absence of other signs, such as cheilosis or the typical glossitis, unless it responded to treatment with riboflavin.

I would, however, advocate most strongly that those interested should acquire an accurate picture of the signs indicative of this deficiency, so that large quantities of this expensive vitamin preparation, which will presumably be so valuable in post-war Europe, will not be given empirically or unnecessarily, and considerable time will not be wasted in investigating signs that have no real diagnostic value.

Summary

An attempt has been made to elucidate early ocular signs due to riboflavin deficiency. Previously, circumcorneal injection has been given an unduly prominent place by other workers, whereas corneal vascularization is a more reliable sign. This is of a distinctive type, consisting of fine streamer-like centripetally arranged vessels invading all round the cornea in both eyes.

The normal anatomy of the part of the eye involved has been described, and other pathological conditions which might give comparable appearances have been briefly discussed.

An investigation of the effect of administration of nicotinic acid as a possible cause of circumcorneal injection has been described.

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In spite of outbreaks of small-pox in surrounding territories, since Feb., 1941, not a single case has been reported within the borders of Southern Rhodesia, yet between 1937 and Feb., 1941, the colony had over 2,600 detected cases of small-pox, almost entirely among natives, though the disease was generally of a mild type. It is worthy of note that a vigorous vaccination campaign has been carried out by the Public Health and Native Departments, as a result of which 400,000 natives (nearly a quarter of the colony's native population) were vaccinated. The Public Health Department now has a trained unit consisting of health inspectors and native vaccinators who systematically ensure effective vaccination. Last year the unit vaccinated 147,000 people. When, in Oct., 1941, small-pox broke out in Francistown, Bechuanaland, a few miles across the Rhodesian border, the unit carried out a vaccination campaign along the border for hundreds of miles and not a single case of small-pox developed on the Rhodesian side.