Clinical Manifestations of Ariboflavinosis*

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SINCE the signs of riboflavin deficiency in human beings have been identified, it has become evident that this avitaminosis is exceedingly common and that its recognition is quite important in estimating the nutritional state. The facial and labial lesions of ariboflavinosis contribute largely to the typical facies of classic pellagra and with glossitis constitute the picture of "pellagra sine pellagra." Stannus [1] in 1912 described "angular stomatitis" associated with glossitis as "pellagra fruste." Goldberger and his collaborators [2, 3] noted the labial lesions and facial seborrhea occurring in the absence of typical dermatitis and suspected the influence of two distinct dietary factors in pellagra. Many other observers have described similar types of localized dermatitis of the face with "perleche" and glossitis curable with yeast.[4-8] Moore [8] found that nicotinic acid did not cure this syndrome but that autoclaved yeast was effective and concluded that deficiency of some other factor than nicotinic acid was the cause. Oscular disturbances in association with sore tongue, sore mouth, inflammation of the nasal mucosa, and at times dermatitis of the genitalia have been stressed by observers in the tropics for a century.[9-11] Moore [8, 11, 12, 13, 14] has described this syndrome in detail; his illustrations show that the facial and oral lesions are typical of ariboflavinosis.

It is recognized that beriberi and pellagra are major syndromes of B group avitaminosis resulting from prolonged subtotal deficiency of the whole B complex. The factors contributing to the development of endemic ariboflavinosis are probably identical. A diet containing a marked excess of carbohydrate over the amount of vitamin necessary for the utilization of the energy derived from it is most important. Defects in absorption, storage, and utilization of the vitamins are almost equally effective. Increased metabolic requirement in the sense of increased derivation of energy from carbohydrate, in the presence of a relatively fixed vitamin intake, is a common source of disease. Vomiting, diarrhea, and edema of the gastrointestinal tract are frequent causes of poor absorption; hepatic disease seems to be an important factor in failure of storage and utilization. Unusual physical exertion, pregnancy, fever, hyperthyroidism, alcoholism, and therapeutic administration of large amounts of dextrose intravenously are common causes of increased utilization of energy. Aside from dietary selection, the factors which determine the predominant avitaminosis in a given case are often obscure.

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Thiamin, nicotinic acid, and riboflavin are components of coenzymes essential to the intermediate metabolism of carbohydrate, when any one of the three vitamins is exhausted from failure of replacement, or possibly when there is a marked failure of balanced intake of the three, a complex disturbance of carbohydrate metabolism results. In addition to coenzyme activity at various stages of the dehydrogenation of hexoses, riboflavin is the active fraction of the yellow respiratory ferment of Warburg. The processes of intracellular respiration are dependent on it and it is thought to be ubiquitous in living cells. Because of its multiple functions it is not surprising that deficiency of riboflavin should be frequent and that the manifestations of deficiency should be varied. There is evidence that other vitamins of the B group have a definite influence on the utilization of riboflavin. Very frequently the administration of large amounts of nicotinic acid to pellagrins maintained on an inadequate diet causes the rapid development of signs of ariboflavinosis after the cure of typical pellagrous glossitis and dermatitis.[15] This phenomenon suggests that the biochemical activity of nicotinic acid involves the utilization of riboflavin, there being as yet no clinical evidence that the converse is true. In certain cases of ariboflavinosis, treatment with riboflavin produces only partial cure of cheilosis and superficial vascular keratitis, the addition of vitamin B6 causes rapid completion of healing.[16] In other instances cure of cheilosis typical of riboflavin deficiency has been brought about by the administration of vitamin B6 alone.[17] There is reason to believe that vitamin B6 mobilizes riboflavin from storage or dissociates it from some combination which is not physiologically active.[16] Pantothenic acid may have a similar action.[16, 18]

Almost nothing is known of the pathology of ariboflavinosis. Lesions of the skin and mucous membranes may be due to local disturbances of cellular nutrition and respiration. Changes in the eyes are best explained as compensatory phenomena to local cellular anoxemia. Bessey and Wolbach [19] suspected that vascularization of the cornea was such a response, they suggested that the normal respiration of the avascular corneal tissues depends on the transport of oxygen from the epithelium to the deeper layers by riboflavin. In the absence of an adequate supply of the vitamin in the cells of the cornea, anoxemia results and capillaries invade the tissues to supply oxygen directly from erythrocytes. It is likely that there is etiological as well as apparent similarity between the fatty infiltration of the liver which occurs in animals deprived of riboflavin and the fatty liver of fatal pellagra.[20, 21] Anemia is much less frequent in ariboflavinosis than in pellagra and there is no anemia from lack of the vitamin when the diet contains an adequate amount of iron.[22] Gastric achlorhydria has been present in approximately 50 per cent of personally observed instances of ariboflavinosis but apparently has not the direct relation to this syndrome that it has to endemic pellagra. It may have much influence on the riboflavin requirement of the individual and on the tendency to relapse.

SYMPTOMS AND SIGNS OF RIBOFLAVIN DEFICIENCY

The symptoms of riboflavin deficiency are numerous and many are common to all avitaminoses. Nervousness, irritability, anorexia, gastric discomfort, and ready fatigue are entirely nonspecific and probably are the result of multiple deficiencies. Soreness of the lips and tongue and dysphagia from tenderness of the tongue and fauces are characteristic. There is not the sensitiveness to hot or highly seasoned food that is

present in nicotinic acid deficiency, nor is there the severe dysphagia due to esophagitis. Pruritus of the vulva or scrotum may be present. In more than half the cases of ariboflavinosis which we have observed, ocular symptoms have preceded any others, they have been present at some time in over 90 per cent. Photophobia, burning and itching of the eyes, a sensation of eyestrain or rapid visual fatigue, poor distant vision and blurred vision in poor light or twilight are specific symptoms. Occurring in the absence of gross refractive error or conjunctival infection, they are highly suggestive of ariboflavinosis. The similarity of these complaints to those occurring in vitamin A deficiency has led to much confusion in their interpretation.[23, 24]

The physical signs of ariboflavinosis are specific and there is a rich experimental background for their correlation with lesions produced in various species of animals. No observer had separated them from the syndrome of endemic pellagra prior to the report of Sebrell and Butler [25] on the lesions occurring in a group of patients maintained on an experimental diet exceedingly poor in riboflavin but well supplemented with other vitamins. Under the conditions of their experiment the first sign to appear was cheilosis. There was maceration at the commissures of the lips with redness and some desquamation of the lips along the line of closure. Redness spread to the buccal surfaces of the lips, fissures developed at the commissures. Mild seborrheic dermatitis occurred in the nasolabial folds, on the alae nasi, and occasionally on the ears and eyelids. Later observations have shown that fissures of the commissures of the eyelids may develop, and that indolent ulcerations of the nasal septum are not infrequent, fissures sometimes occur on either side of the septum at the nasal orifices. The secretion of the sebaceous glands of the face seems to be altered so that inspissated, almost hair-like comedones are apt to develop over the forehead, malar eminences, nose and chin—this "shark-skin eruption" frequently has been emphasized in the description of classic pellagra. The tongue becomes clean, the papillae flattened or mushroom-shaped rather than atrophic as in nicotinic acid deficiency. The color of the tongue is characteristic, the normal pink is replaced by a purplish-red or magenta quite different from the scarlet of nicotinic acid deficiency.[26, 27] The color and texture of the tongue are important in differentiating ariboflavinosis from nicotinic acid deficiency. In addition to localized seborrheic lesions of the face and ears, generalized seborrheic dermatitis may be a manifestation of riboflavin deficiency; we have seen 4 patients in whom extensive seborrhea healed without local treatment during the administration of riboflavin for the cure of coincident specific oral and ocular lesions. More rarely dry, brown, itching dermatitis of the hands and scrotum or vulva present in patients with typical cheilosis and glossitis has healed during treatment instituted for typical signs of riboflavin deficiency. The specific nature of such dermatoses is yet to be determined.

OCULAR MANIFESTATIONS

The ocular manifestations of riboflavin deficiency are of special interest and importance. There have been many references to the occurrence of visual disturbances in association with signs now known to be due to ariboflavinosis. Time does not permit discussion of the extensive experimental work of Day and his collaborators,[28-33] of O'Brien,[34] and others. For years it has been known that so-called ophthalmia as well as cataract could be produced in rats by a diet deficient in the heat stable fraction of yeast. Bessey and Wolbach [19] first used the slit lamp to study the

progress of ocular changes in rats deprived of riboflavin, and followed their observations during life with india-ink injection and histological examination post-mortem. They found that superficial vascularization of the cornea was the earliest sign of riboflavin deficiency. As avitaminosis progressed, superficial and interstitial nebulae developed in the cornea, later there was invasion of the deeper layers by newly formed capillaries until extensive vascular networks were produced. The process could be arrested at any time by the administration of riboflavin, new vessels rapidly became empty of blood but remained visible for many months. These observations were confirmed in all essential details by the almost simultaneous report of Eckardt and Johnson.[35] The majority of clinical students of nutritional disease have been impressed with the prevalence of ocular complaints in patients presenting evidence of B group vitamin deficiency. Reference has been made to numerous observers in the tropics. Spies, Vilter, and Ashe[23] noted histories of visual impairment or burning of the eyes associated with conjunctivitis or mydriasis in 70 per cent of their patients. Spies studied a group of 50 patients with ocular complaints.[24] While these observers were inclined to attribute the symptoms and signs to vitamin A deficiency, they noted that a number of patients were relieved by the administration of riboflavin. Pock-Steen[36] gave an accurate description of ocular symptoms occurring in a rather large group of patients with sprue. This author suspected that they might be due to riboflavin deficiency and was able to secure rapid cure with small amounts of the vitamin in over 90 per cent of cases.

During the past year and a half our group has paid special attention to the ocular complaints of patients with oral signs of ariboflavinosis and to the examination with a slit lamp of their eyes at various stages in the development of mouth and skin lesions, as well as during periods of treatment. Many of these individuals were allowed to relapse after cure had been effected with riboflavin. Corneal vascularization was found to be constantly present when other signs of ariboflavinosis could be recognized except in a few patients with marked arcus senilis. All grades of vascularization were observed, and it seems possible to reconstruct the whole sequence of events from the many fragments of the picture. At the same time we studied the eyes of a group of apparently normal persons who complained only of visual disturbances, particularly photophobia, ocular fatigue, and dim vision not improved by correction of refractive errors. Among these were seen the earliest stages of corneal vascularization as well as several well advanced instances of keratitis. Mydriasis and defects of accommodation were common in this group and probably contributed to the symptoms of photophobia and poor distant vision.[27, 37]

The earliest and most frequent sign of ariboflavinosis is slight circumcorneal congestion, frequently visible with a hand lens or ophthalmoscope before it can be seen by the unaided eye. In such cases the slit lamp shows proliferation and marked congestion of the limbic plexus; there are many newly formed capillaries which obliterate the normal avascular zone between the plexus and the sclero-corneal junction. Each scleral digitation is apt to be outlined by capillaries which form a more or less complete arcade but do not yet encroach on the cornea. Within a few days, sometimes only one or two, empty capillaries can be seen sprouting from the apices of the loops of the limbic arcade; these "sprouts" lie just beneath the epithelium and grow centripetally; in from 2 to 4 days clumps of red blood cells circulate through them making

irregular, jerky progress; at this stage the deeper efferent limb of the loop cannot be clearly seen. Such vessels tend to grow rapidly and form anastomoses with adjacent capillaries to form a secondary arcade lying within the cornea. From this, secondary capillary sprouts develop and grow centripetally, anastomosing freely until an extensive superficial plexus is formed which may cover the peripheral two-thirds of the cornea. Much later, deeper vessels, which invade the substantia propria at all levels, spring from the limbic plexus, and eventually a scanty posterior plexus may be formed which lies just proximal to Descemet's membrane. It seems characteristic of the keratitis of ariboflavinosis that vascularization is predominantly anterior. In long standing cases which have undergone repeated relapses, very extensive corneal vascularization may be seen with large vessels at all levels, but a posterior plexus is never prominent. Early in some cases, but usually after prolonged deficiency, diffuse nebulae develop at various levels; quite frequently there are fine superficial punctate opacities. A few patients with extensive vascularization had large scars, almost certainly the result of corneal ulcers.

The response of nutritional keratitis to treatment has been prompt and often spectacular. The stage of congestion and proliferation of the limbic plexus was identified as a sign of deficiency only after the plexus had been seen to return to a normal state after the administration of riboflavin. Depending on the extent of vascularization and the size of the vessels present, it may require from 2 to 10 days for occlusion to occur. Large vessels, the result of very chronic deficiency or complicating corneal ulcers, may never become occluded. The first evidence of healing is interruption of the columns of blood in the capillaries producing a "beaded" appearance; 2 or 3 days later the vessels are empty or contain scattered clumps of red cells which are stationary and eventually disintegrate. The empty vessels remain visible for at least a year. Nebulae resolve slowly, often requiring 3 weeks for absorption.

Recently Johnson and Eckardt [38] reported the cure of rosacea keratitis in 32 of 36 patients treated with riboflavin; in 9 cases cutaneous rosacea was also present. These authors did not mention the incidence of oral lesions of ariboflavinosis but did note the similarity of the corneal vascularization to that observed in rats with experimental riboflavin deficiency. It is quite likely that the syndrome designated "rosacea" by dermatologists and ophthalmologists would be called ariboflavinosis by an observer interested in nutritional disease.

Iritis has been seen in 5 instances where keratitis and cheilosis were present, in each case iritis subsided during treatment with riboflavin. Accumulations of pigment, probably of pigment bearing wandering cells, on the anterior surface of the iris was observed in 24 of our patients. On grey irises this pigment occurred in irregular clumps which we cannot distinguish from "hazel spots"; brown irises have a shaggy, smoothed-out appearance due to veiling of the normal architecture. Such pigmentation was recognized as abnormal only after it was seen to disappear during treatment.

The amount of riboflavin required for satisfactory treatment in any case is conditioned by the adequacy of the diet which can be furnished and by the ability of the patient to extract dietary riboflavin from food sources. Under experimental conditions with a diet extremely poor in the vitamin, 5 mg.* daily has been the average dose required

* Riboflavin employed in our investigations has been the pure crystalline synthetic vitamin furnished by Merck & Co., E. R. Squibb & Sons, and the Winthrop Chemical Co. Riboflavin-sodium for injection was furnished by Merck & Co.

for rapid cure, in the presence of diarrhea, irreversible gastric achlorhydria or severe hepatic disease, 10 or even 15 mg. a day may be required when given by mouth. Under uncontrolled conditions with a tolerably adequate diet, 3 mg. daily is adequate for cure and maintenance of the great majority of patients. In extremely depleted patients with polyavitaminosis of severe grade, 10 mg. daily of riboflavin-sodium given intravenously is not an excessive amount.

It is almost superfluous to say that dietary treatment should never be neglected. Ariboflavinosis is the syndrome of " pellagra sine pellagra " and though the distinctive manifestations may be those of riboflavin deficiency alone, B group deficiency probably exists in every instance. Dietary habits, economic stress, or coincident disturbance of the gastrointestinal apparatus may determine the predominant avitaminosis.

When it can be administered and digested, the usual 60 to 90 gm. daily ration of yeast curative for pellagra contains ample amounts of riboflavin as well as the other vitamins needed for adequate nutrition. It is doubtful whether riboflavin should be given over long periods without making sure that other members of the B group are supplied by food, by yeast or the pure vitamins.

The recognition of ariboflavinosis as a syndrome is of much interest, it is of even more importance. Early corneal vascularization is visible with a slit lamp before any gross signs such as cheilosis or glossitis have developed. This method of examination is probably the most delicate test available for deficiency of the B group of vitamins.

SUMMARY

Since the signs of " pellagra sine pellagra " have been shown to be due to deficiency of riboflavin in the diet, it has become possible to correlate many observations on nutritional disease which have seemed contradictory. Ariboflavinosis, like pellagra and beriberi, is a manifestation of B group avitaminosis. The specific signs probably result from a complex disturbance of the coenzyme functions of the B vitamins as a group, to which is added failure of the activity of riboflavin in intracellular oxidation.

Riboflavin deficiency is characterized by photophobia and dimness of vision at a distance and in dim light; cheilosis, seborrheic lesions about the ears and nose, and a specific sort of glossitis. Examination of the eyes may show mydriasis and defects of accommodation. The earliest and most constant finding is a superficial vascularization of the cornea. This may progress to severe interstitial keratitis. Therapeutic tests have shown that rosacea keratitis also is due to deficiency of riboflavin. A few patients with syphilitic keratitis have shown remarkable improvement during the administration of this vitamin.

Recognition of the early ocular signs of riboflavin deficiency offers an easy method of identifying B group avitaminosis at a stage when no gross signs are present.

REFERENCES

1. Stannus, H. S. Pellagra in Nyasaland. *Tr. Soc. Trop. Med. & Hyg.*, 5:112, 1912.

2. Goldberger, J., and Tanner, W. F. A Study of the Pellagra-preventive Action of Dried Beans, Casein, Dried Milk and Brewer's Yeast with a Consideration of the Essential Preventive Factors Involved. *Pub. Health Rep.*, 40:54, 1925.

3. Goldberger, J., Wheeler, G. A., and Sydenstricker, E. A Study of the Diet of Non-pellagrous and of Pellagrous Households in Textile Mill Communities in South Carolina in 1916. *J.A.M.A.*, 71:944, 1918.

4. Wright, E. J. Disease Due to A and B Avitaminosis in Sierra Leone. *West African M. J.*, 2:127, 1928.

5. Fitzgerald, G. H. An Outbreak of Exfoliative Glossitis in an Assam Jail. *Indian M. Gaz.*, 67:556, 1932.

6. Landor, J. V., and Pallister, R. A. Avitaminosis B_2. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 29:121, 1935.

7. Aykroyd, W. R., and Crishnan, B. G. Stomatitis Due to Vitamin B_2 Deficiency. *Indian J. M. Res.*, 24:411 (Oct.), 1936.

8. Moore, D. F. Retrobulbar Neuritis with Pellagra in Nigeria. *J. Trop. Med. & Hyg.*, 42:109 (Apr. 15), 1939.

9. Clarke, R.; cited by Leitch, J. N. *Dietetics in Warm Climates.* London, Harrison, 1930, p. 368.

10. Strachan, H.; cited by Leitch, J. N. *Dietetics in Warm Climates.* London, Harrison, 1930, p. 368.

11. Moore, D. F. Partial Loss of Central Acuity of Vision for Reading and Distance in School Children and Its Possible Association with Food Deficiency. *West African M. J.*, 3:46, 1930.

12. Moore, D. F. Nutritional Retrobulbar Neuritis Followed by Partial Optic Atrophy. *Lancet*, I:1225 (May 22), 1937.

13. Moore, D. F. Pellagra or Pellagra-like Conditions in Association with Deficiency of Vitamin A. *J. Trop. Med. & Hyg.*, 43:190 (July 15), 1940.

14. Moore, D. F. Personal communication.

15. Schmidt, H. L., Jr., and Sydenstricker, V. P. Nicotinic Acid in the Prevention of Pellagra. *J.A.M.A.*, 110:2065 (June 18), 1938.

16. Singal, S., Briggs, A. P., and Sydenstricker, V. P. Unpublished observations.

17. Smith, S. G., and Martin, D. W. Cheilosis Successfully Treated with Synthetic B_6. *Proc. Soc. Exper. Biol. & Med.*, 43:660 (Apr.), 1940.

18. Spies, T. D., Stanberry, S. R., Williams, R. J., Jukes, T. H., and Babcock, S. H. Pantothenic Acid in Human Nutrition. *J.A.M.A.*, 115:523 (Aug. 17), 1940.

19. Bessey, O. A., and Wolbach, S. B. Vascularization of the Cornea of the Rat in Riboflavin Deficiency, with a Note on Vascularization of the Cornea in Vitamin A Deficiency. *J. Exper. Med.*, 69:1 (Jan.), 1939.

20. Field, H., Jr., and Wise, E. C. Fatal Probable Riboflavin Deficiency in Man. *J. Clin. Investigation*, 18:474 (July), 1939.

21. Kisch, F. Vitamin B_2 (Lactoflavin) in der Behandlung funikularer Myelose bei Perniziöser Anämie. *Wien. med. Wchnschr.*, 87:194 (Feb. 13), 1937.

22. Sebrell, W. H., and Butler, R. E. Riboflavin Deficiency in Man (Ariboflavinosis). *Pub. Health Rep.*, 54:2121 (Dec. 1), 1939.

23. Spies, T. D., Vilter, R. W., and Ashe, W. F. Pellagra, Beri-beri and Riboflavin Deficiency in Human Beings. *J.A.M.A.*, 113:931 (Sept. 2), 1939.

24. Spies, T. D. A Note on the Ocular Symptoms and Signs Occurring from Malnutrition in Human Beings. *Am. J. M. Sc.*, 198:40 (July), 1939.

25. Sebrell, W. H., and Butler, R. E. Riboflavin Deficiency in Man, a Preliminary Note. *Pub. Health Rep.*, 53:2282 (Dec. 30), 1938.

26. Jolliffe, N., Fein, H. D., and Rosenblum, L. A. Riboflavin Deficiency in Man. *New England J. Med.*, 221:921 (Dec. 14), 1939.

27. Kruse, H. D., Sydenstricker, V. P., Sebrell, W. H., and Cleckley, H. M. Ocular Manifestations of Ariboflavinosis. *Pub. Health Rep.*, 55:157 (Jan. 26), 1940.

28. Day, P. L., Langston, W. C., and O'Brien, C. S. Cataract and Other Ocular Changes in Vitamin G Deficiency; Experimental Study on Albino Rats. *Am. J. Ophth.*, 14:1005 (Oct.), 1931.

29. Langston, W. C., and Day, P. L. Nutritional Cataract in the Norway Rat. *South. M. J.*, 26:296 (Feb.), 1933.

30. Langston, W. C., Day, P. L.. and Cosgrove, K. W. Cataract in the Albino Mouse Resulting from a Deficiency of Vitamin G (B_2). *Arch. Ophth.*, 10:508 (Oct.), 1933.

31. Day, P. L., and Langston, W. C. Further Experiments with Cataract in Albino Rats Resulting from the Withdrawal of Vitamin G (B_2) from the Diet. *J. Nutrition*, 7:97 (Jan.), 1934.

32. Langston, W. C., and Day, P. L. Arrest of Nutritional Cataract in Albino Rats by the Use of Vitamin G (B_2). *South. M. J.*, 27:170 (Feb.), 1934.

33. Day, P. L., Darby, W. J., and Langston, W. C. Identity of Flavin with the Cataract-preventive Factor. *J. Nutrition*, 13:289 (Apr.), 1937.

34. O'Brien, C. S. Experimental Cataract in Vitamin G Deficiency. *Arch. Ophth.*, 8:880 (Dec.), 1932.

35. Eckardt, R. E., and Johnson, L. V. Nutritional Cataract and Relation of Galactose to Appearance of Senile Suture Line in Rats. *Arch. Ophth.*, 21:315 (Feb.), 1939.

36. Pock-Steen, P. H. Eye Symptoms in Patients with Leiodystonia and Sprue: Aknephaskopia. *Geneesk. tijdschr. v. Nederl.-Indië*, 78:1986 (Aug. 8), 1939.

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

38. Johnson, L. V., and Eckardt, R. E. Rosacea Keratitis and Conditions with Vascularization of Cornea Treated with Riboflavin. *Arch. Ophth.*, 23:899 (May), 1940.