BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 22 1944

SOME PROBLEMS IN RIBOFLAVIN AND ALLIED DEFICIENCIES*

BY

HUGH S. STANNUS, M.D., Ph.D., F.R.C.P.

I have chosen as the subject of these lectures one which I think may be discussed with advantage just now when nutrition is a matter very much to the forefront in Britain, when the problem of malnutrition among the native inhabitants of our Colonies is still awaiting solution, and when plans for feeding the starving peoples of enemy-occupied countries are being considered. First, I shall discuss a syndrome recognized many years ago and then later further defined, and its relation to the condition to which the term "ariboflavinosis" was assigned by Sebrell and Butler (1938). I shall then suggest a tentative explanation of the pathogenesis of the signs and symptoms of riboflavin deficiency and of their peculiar localization, based on an anatomico-physiological consideration of the capillary vascular system. In this abridged form it will not be possible to do more than give an outline of my thesis, and much detail and full references will perforce be omitted.

Early Personal Observations

Just over 30 years ago—in 1912-13—I published an account of the first outbreak of pellagra to be recognized in Africa, apart from Egypt, when I was afforded the opportunity of proving for the first time that that disease had no intrinsic relationship with the consumption of maize, as the subjects, long-term prisoners in Nyasaland, had been maintained on rice. I drew attention to a group of symptoms which tended to precede the onset of the more classical signs of pellagra by many months or which, indeed, persisted without those signs appearing. This group of symptoms included soreness of the tongue and lips, with a very characteristic lesion at the corners of the mouth, associated with a similar condition about the nostrils, the palpebral fissures, the free border of the prepuce, the vulva and anus, together with a dermatosis of the scrotum, often also involving the skin of the adjacent part of the thigh.

More important still, it was found that the syndrome above described, in its less fully developed form limited usually to the affection of the corners of the mouth, lips, and tongue, was not uncommon among the general native population. Further inquiries elicited the fact that this affection occurred in other parts of East Africa, and two interesting points came to light—first, that the condition, associated with obscure nervous symptoms, was common among native children at a mission boarding-school in Zanzibar; and, secondly, that their symptoms cleared up when they returned to their villages for the long vacation.

I had noted among my prison cases various neurological symptoms, including deafness and diminution of vision with loss of pupillary sphincter tone, but did not, at that time, associate them with the syndrome under discussion. I believed that pellagra and this syndrome were the result of dietetic deficiency; but these were early days, just about the time when Funk was engaged in preparing Factor B and when the word "vitamine" was introduced.

The importance of these early observations lay in the fact that this was the first time that attention had been drawn to the occurrence of this group of symptoms, due to a dietetic deficiency—dissociated from pellagra. Each, as a symptom occurring in pellagra, was in no way new, as a perusal of the writings of the older pellagrologists from Casal (1730) downwards will show.

In 1911 I drew attention to a long-forgotten description by Strachan (1888) of a condition among natives in Jamaica, believed by him to be "malarial multiple peripheral neuritis," in which mention is made of practically all the same symptoms; and in 1930 I pointed out the resemblances between a condition described by Scott (1918) as "central neuritis" of toxic origin, among Jamaican labourers, and the syndrome under discussion.

Collected Observations

Later, in 1936, I collected together and reviewed a number of interesting observations which had been published in the meantime upon conditions which I considered were akin to the original syndrome. I used the expression "pellagra-like conditions" to focus attention upon malnutrition as the basis of causation. The close connexion was obvious then, as it is now, when we recognize the close relationship between nicotinic acid and riboflavin in the vitamin B₂ complex and the relation of each to pellagra.

Among these observations were a number which had reference to an affection only of the tongue, lips, and the angles of the mouth. These I shall not consider further. (Blacklock, Sierra Leone, 1925; Jamin, Tunisia, 1925; Nogue, Dakar, 1925; Mathis and Guillet, Dakar, 1925; Gayot, Dakar, 1920; Brocq and Paultrier, Fréjus, 1928, 1939; also Barlovatz, Congo, 1940.) It will not be possible either to discuss here the very interesting condition occurring among infants in East and West Africa and elsewhere which I have referred to as infantile pellagra, but in which riboflavin deficiency probably plays a major part.

The remainder, to which have been added a few published more recently, are shown in the Table (under D) for the sake of brevity. They constitute, I believe, a series showing manifestations of the same syndrome in more or less complete form. The disparities may be explained in part, I think, by the fact that in some cases the descriptions are not very full and are obviously incomplete, the period of observation is short, and opportunities for exhaustive examination are lacking. In other cases want of exact parallelism may be due to variations in the comparative intensity and duration of the causative process.

Fitzgerald Moore's observations are of particular importance, for to him belongs the credit of recognizing that the disease which was rendering thousands of natives nearly blind was due to a dietetic deficiency and was amenable to treatment with marmite. His first paper was published in 1930. From this and those published subsequently, and a number of personal communications, a fairly complete picture of the affection can be drawn—one that reproduces the original syndrome described, but unassociated in any way with the dermal and other classical symptoms of pellagra. The second communication of importance was that by Landor and Pallister in 1935. They

* The Lumleian Lectures (abridged) delivered before the Royal College of Physicians of London, April 18 and 20, 1944.

Table showing Manifestations of the Syndrome according to Various Authors

			Tongue	Lips	Angular stomatitis	Nostrils	Canthi	Prepuce	Vulva	Anus	Scrotum	Groin	Face	Body	Vision	Hearing	C.N. System	Mental	Conjunctiva	Photophobia	Limbic Plexus	Corneal Vascularization	Mydriasis
A. Stannus	Central Africa	1911-13																					
B. Strachan	Jamaica	1888																					
C. Scott	Jamaica	1918																					
D. Bradley	Seychelles	1928																					
Wright	Sierra Leone	1928																					
Fitzgerald Moore ..	Nigeria	1930																					
Fitzgerald	Assam	1932																					
Nicholls	Ceylon	1933																					
Dumont	Congo	1934																					
Landor and Pallister ..	Malay	1935																					
St. John	Barbadoes	1936																					
Aykroyd <i>et al.</i> ..	India	1936																					
Meager	Solomons	1936																					
Browne	British Guiana	1939																					
Wilkinson and King* ..	Hong Kong	1944																					
E	Spain																						
F	United States	1938-41																					

* Published since these lectures were delivered.

described a condition which practically duplicated that recorded by Fitzgerald Moore. They showed that recovery took place when treatment with autoclaved yeast or autoclaved marmite was given. Fitzgerald Moore's cases also responded to the same preparations. This result excluded vitamin B₁ as a factor in causation. Fitzgerald Moore was also able to show that vitamin A played no part, and later that nicotinic acid had no curative effect. That author was more particularly interested in the ophthalmological condition. In early cases complaining of dimness of vision, with, or with a history of, sore lips and sore tongue, no changes were found in the fundi. Later, pallor of the temporal halves of the disks was noted, in some optic atrophy, in others signs of optic neuritis. Central scotoma and some retraction of fields were demonstrated in a few cases. Loss of pupillary tone and photophobia were also noted. The nervous symptoms, apart from loss of visual and auditory acuity, consisted of some mental dullness, a sense of muscular weakness, ataxia, and paraesthesiae.

It is of interest to recall the fact that Goldberger and Tanner in 1915 and 1925 produced experimentally some of the symptoms of this syndrome and referred to them as "pellagra sine pellagra," as I had previously done, but they were apparently unaware of my observations. It is also of interest to remark the similarity of the signs and symptoms in animals—the rat and the dog—but space will not allow of their discussion here.

At the end of 1938 Sebrell and Butler published their "preliminary note" on "Riboflavin Deficiency in Man." Nicotinic acid and riboflavin had then been isolated from vitamin B₂ complex. The results of experiments on animals fed riboflavin-free diets and certain observations on nicotinic-acid-treated pellagrins led these observers to repeat Goldberger and Tanner's feeding experiments. Of 18 women so treated 10 developed in from 94 to 130 days lesions on the lips, at the angles of the mouth, in the vestibule of the nose, etc., comparable to those described by Goldberger and Tanner and those described by myself—a fact which the authors immediately recognized. These lesions cleared up under treatment with riboflavin.

Thus then was given the first demonstration of the relationship of some part of the original syndrome with riboflavin deficiency. These authors suggested that "the term ariboflavinosis be added to the nomenclature of the vitamin-deficiency diseases as a designation for the clinical condition due to riboflavin deficiency." Since there is reason to believe that death ensues long before the advent of a-riboflavinosis, I prefer to use the term "hypo-riboflavinosis."

During the following three or four years other symptoms were added to the original "ariboflavinosis" syndrome by

observers in the United States, chief among them being Sydenstricker and his colleagues, the diagnostic criterion in all cases being a response to riboflavin therapy.

Again, though there are differences between the symptoms and signs enumerated under ariboflavinosis and those included in the older syndrome, I think that they may be looked upon as differences in degree and that they may be explained along the lines above mentioned (see Table, F). Further, many of the groups of symptoms, combined into a series of overlapping syndromes due to malnutrition during the Civil War of 1936-9—described by Spanish observers although, as they stated, unfamiliar to them—reproduced those which I have shown were recognized years before (see Table, E). The symptoms will be dealt with in greater detail when I come to speak of their pathogenesis.

Although there are reasons, on epidemiological grounds, for believing that all the signs and symptoms I have grouped together should be considered as parts of a single clinical entity due to riboflavin deficiency, we cannot at the present time exclude the possibility that some other factor—perhaps some other member of the vitamin B₂ complex—plays a part. For the sake of brevity, however, in what follows I shall speak only of hypo-riboflavinosis.

The Action of Riboflavin

Riboflavin is generally held to be present in the cells of every tissue of the body. Like other members of the B group of vitamins—not in themselves enzymes or catalysts, but components of chemical combinations, known as coenzymes, which in conjunction with specific proteins, the apo-enzymes, form a number of systems essential for the breakdown of carbohydrates with the release of energy little by little—riboflavin, combined in the form of a flavoprotein, acts by alternately accepting and releasing two atoms of hydrogen, and thus participates in a number of reactions in connexion with carbohydrate metabolism, and among them that which forms the link between the anaerobic dehydrogenase system and the aerobic cytochrome : cytochrome-oxidase : oxygen system. Oxidation may be defined as the change of an atom or ion from a state of lower valence to a state of higher valence. Reduction is the reverse. Oxidation in the sense of biological oxidation of carbohydrate may be effected by the addition of oxygen, by the removal of hydrogen, or by the withdrawal of one or more electrons (or negative charges), without the equivalent transfer of oxygen or hydrogen.

All the stages of the complicated series of processes involved in the release of energy from the carbohydrate molecule are not well understood, but the following schematic set of equations will serve to demonstrate the principle involved and to

indicate the close association of riboflavin with the utilization of carbohydrate and oxygen.

Since riboflavin is associated with intracellular catalytic processes any deficiency may be expected to give rise to a metabolic disturbance in every cell of the body.

In the past it has been customary when thinking of any tissue merely to assume a cellular deficiency of riboflavin without considering how that deficiency comes about. I propose, therefore, to discuss some part of this problem.

The Role of the Capillary System

Perhaps we do not always realize that the vascular system has been developed for a single purpose—that of carrying to the immediate environment of each individual cell all the essentials to satisfy its needs, thus creating an environment comparable to that of a unicellular organism. The actual living parts of complex organisms are embedded in a fluid matrix constituting an internal environment the constitution of which normally remains constant—a condition referred to as homeostasis or homeokinesis. Claude Bernard (1878) was the first to realize this truth, crystallized in his expression—“*La fixité du milieu intérieur est la condition de la vie libre.*” This theme was further developed by Cannon (1930), and later was the subject of discussion by Barcroft (1934). Mechanisms have been developed in the body whose sole object is the preservation of this constant. As stated by Cannon: “The membranes which separate the vascular from the interstitial compartment and those which separate the latter from the intracellular compartments have peculiarities of permeability which maintain an unequal distribution of solutes in the three compartments.” Exchanges in one or other direction are effected by vascular adjustments controlled, it is now generally recognized, by a “capillariomotor system,” independent of the rest of the vasomotor system, by hormones, by local metabolites, etc.

The capillary system is therefore of prime importance, its welfare essential for the maintenance of the tissues in health; yet when Krogh (1929) published his monograph, *The Anatomy and Physiology of the Capillaries*, he remarked: “The capillaries constitute the most essential part of the circulatory system,” but added, “They have been neglected in an extraordinary way.”

Much work has been done on the subject by a number of investigators, including Dale (1918–19), Krogh (1929), Lewis (1927), Bordley *et al.* (1938), Wright and Duryee (1933), the Clarks (1931–2), Sandison (1928), Cobb (1927–32), Zweifach (1937–40), Sanders, Ebert and Florey (1940), etc.; but space forbids anything but mention of their names.

I cannot here go into more detail, but must be content to point out how *great* is the part played by the capillary system, how *many* its functions in the economy of the organism, and how *vast* its field of action.

To give a single example from Krogh: he calculated that the capillaries supplying the muscles of an adult man, which number 1,350 per square millimetre in transverse section, would measure 100,000 kilometres if joined end to end—i.e., would go twice round the world. Their surface would be 6,300 square metres. A simple calculation shows that if packed into a solid mass these endothelial cells would form an organ of

some size. The time has passed when the capillary endothelium was looked upon by the older physiologists as a passive, inert membrane, like a piece of gelatin governed only by simple physical laws. It is a tissue of great activity; it must need a considerable amount of energy in order to carry on its functions, yet nothing is known concerning the metabolism and respiration of its cells.

Many may have tacitly taken it for granted that a tissue which is in direct contact with the blood stream had merely to pick up what it wanted without any vital process being involved, but this is not consonant with Nature's methods. It may be assumed—and I think the assumption is warranted—that the endothelial cell respires in the same way as the cell of any other tissue, and that for its metabolic processes it must be supplied with sugar, oxygen, and all those other elements essential for cell life, including riboflavin. Having made this assumption, I am going to suggest that in the event of a deficiency in any one of these elements, or in some one of the elements—namely, riboflavin—the capillary endothelium will be one of the first, if not the first, of the tissues to suffer the effects of interference with normal respiration and metabolism. The result of this anoxia, in the wide sense of the term, upon the capillaries is a derangement of function, which I shall refer to as “capillary dysergia,” with the development of loss of tone, dilatation, and decreased flow. This in turn leads to a disturbance in the surrounding *milieu intérieur* and so to a metabolic disorder of the cells of the neighbouring tissue.

It is generally agreed that the relative number of capillaries is such, and their disposition so devised, as to accommodate the metabolic needs of each tissue in the body. This being so, I have suggested that manifestations of riboflavin deficiency will become apparent first in those tissues with high metabolic activity and a high degree of capillarity. By capillarity I mean the relative number of capillaries normally present in a tissue. The signs will be capillary dilatation, obviously only to be determined in some tissues; the symptoms, impaired nutrition and impaired function of the tissues. It is upon this basis that I propose to offer an explanation of the nature and distribution of the signs and symptoms of hypo-riboflavinosis.

(To be concluded)

TWO YEARS OF MILITARY PSYCHIATRY IN THE MIDDLE EAST

BY

H. B. CRAIGIE, M.B., D.P.M.

Lieut.-Col., R.A.M.C.

In his article “Three Years of Military Psychiatry in the United Kingdom” (*B.M.J.*, 1943, 1, 1) Brigadier J. R. Rees has presented a general survey of Army psychiatry in this country, setting out its development and present tendencies. The present article gives a survey of Army psychiatry in its application to an expeditionary force engaged in an active theatre of war.

Development and Organization

The development of a psychiatric organization in the Middle East dates from the appointment in Aug., 1940, of a Consulting Psychiatrist to the Middle East Force. The entry of Italy into the war in May, 1940, had marked the inception of a new phase in the military situation of the Middle East. With the arrival of large and constantly increasing drafts of men from all parts of the Empire it became evident that the provision of an adequate and organized psychiatric service was likely to become a matter of some urgency. The history of the psychiatric organization in the Middle East, originating as above, has been one of continued expansion. Before the arrival of the Consulting Psychiatrist no special facilities existed for the diagnosis and treatment of psychiatric cases, which were of necessity admitted either to the ordinary medical wards of a general hospital or, as in the case of psychotics, to small observation wards attached to two or three of the established military hospitals.