very greatly in size and weight but do differ in the use to which the fore-limb is put. There is evidently a great difference in the extent of the cerebellar area to which impulses concerned with the fore-limb are sent; and the comparison is also useful because it draws attention to the large fraction of the cerebellum which does not seem to be employed in any localized representation of the body and limbs. It shows, in fact, that we are still at the beginning of the story.

Conclusion

I have tried to give a sketch of a method of research on the central nervous system in which rapid advance is possible and in which it is difficult to foresee how far it may not go. But, as with all long-range research nowadays, the advance has been held up until the younger generation of physiologists can come back from the more urgent problems which they have to solve. Some day military or naval or air physiology should form the subject of a future Abrahams lecture. Compared with these problems of life and death the academic study of the nervous system seems to-day of very little consequence. All I can hope is that an account of its progress may serve as a reminder of the things which were important to us in better times, and as a reminder of a Fellow of the College of Physicians who lived when those times were taken for granted as the natural consequence of civilization.

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SOME PROBLEMS IN RIBOFLAVIN AND ALLIED DEFICIENCIES*

BY

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

(Concluded from page 105)

SIGNS AND SYMPTOMS OF HYPORIBOFLAVINOSIS

The mild constitutional symptoms, including the feeling of being "out of sorts," of loss of "pep," of mental and physical fatigue, might thus be explained, as also perhaps symptoms referred to the heart and gastro-intestinal tract.

All the dermal manifestations support my thesis, I believe. The skin has been regarded as a tissue possessing but a relatively small capillary vascularization, associated with a low metabolism, but this is fallacious. The first statement referred to the number of capillary loops per square millimetre which can be counted by Lombard's method of microscopy and left out of consideration the subpapillary plexus—the plexus which gives to the skin its colour and which itself is made up of giant capillaries. The second statement was based on the tissue-slice respiratory method of estimation, when of course the skin was not exercising any of its normally marked activities. The skin as a whole may be affected, or only those areas whose anatomico-physiological design is specialized in some direction, as I pointed out some years ago.

A mild erythema associated with fine desquamation, referred to by Sydenstricker as pityriasis sicca, may be remarked. It is most easily recognized in the skin of the forehead and face, sometimes on the hands, in the fair-skinned individual. In the pigmented skin of the native the erythema cannot be detected, but the desquamation may be noted.

In other cases the change may be obvious only where the skin is very thin, as in the antecubital fossa, or specialized, as in the case of the scrotum and in the transitional type of skin about the orifices of the body—the palpebral fissures, the nares, the free margin of the prepuce, the vulva and anus—giving rise to the lesions I have described.

Sydenstricker two or three years after his first communication on ariboflavinosis mentioned pruritus of the scrotum and vulva,

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

but made no reference to any visible lesion. On the other hand, an excellent photograph of the scrotal condition was reproduced by Spies and Cooper (1937), but with the subscription "pellagrous dermatitis of the scrotum and thighs." The lesions of the prepuce, vulva, and anus do not appear to have been recognized by American observers. Possibly they have not distinguished them from the urethritis, vaginitis, and proctitis which occur in pellagra.

The seborrhoeic lesions about the nose and in the nasolabial folds are a good example of the disturbance in an area of skin which normally possesses a rather different anatomico-physiological arrangement from the rest of the skin. Whether these lesions are of the same nature as those described by Smith, Smith, and Callaway (1941) under the designation "dyssebacia" is uncertain, as they held that the condition they described was not cured by any one of the known vitamin B₂ complex factors but did respond to autoclaved yeast or liver extract.

The affection of the vermilion portion of the lip—cheilosis—is another example of the incidence of the lesion being associated with anatomical specialization, for here the capillary loops are notably very much closer together than in other parts of the skin.

The best description of the changes in the skin capillaries is contained among observations made by Márquez Blasco and Peraíta (1940) upon patients suffering from nutritional deficiencies during the Spanish Civil War. They found that, using a dermal capillaroscope, pathological changes, least marked in simple cases of pellagra, were progressively more accentuated in proportion to the advent and advance of symptoms indicating involvement of the nervous system, including loss of visual and auditory acuity—symptoms which I shall come to shortly.

Angular Stomatitis

The angular stomatitis calls for some words of comment. The term—not a very happy one—was originally used by myself, and seems unfortunately to have persisted. It is difficult to find a better as, so far as I know, there are no words in any language which distinguish between the opening into, and the cavity of, the mouth. Angular stomatitis at least serves to distinguish the lesions so named from "cheilosis," the lesion of the vermilion of the lip, though some American authors—wrongly, I believe—include both under cheilosis.

If the corners of the mouth be examined carefully, with the mouth open but produced into a pout, it will be observed that the vermilion portion of the lips does not encircle the mouth at the angles, but passes internal to the delicate fraenum which has become visible—that, in fact, the lips are prolonged on to the inner side of the cheek. This accounts for another common feature in this condition—namely, the presence on the inner side of the cheek of a linear lesion comparable to the angular stomatitis on the skin outside.

That the lesions of riboflavin deficiency become worse if nicotinic acid be given has been noted by several observers without any explanation. I suggest it is due to the pharmacological vasodilator action of nicotinic acid on an already damaged capillary endothelium.

These lesions are, I believe, characteristic, and with experience I think it may be possible to distinguish them from others produced, it has been suggested, by dentures, etc., and from the condition sometimes to be seen in those with turned-down corners to the mouth, patches of herpes, impetigo, lichen, etc. The introduction of the expression "pseudo-ariboflavinosis" by Ellenberg and Pollack (1942) is, I think, much to be deplored.

This leads me to mention the word "perlèche," a term adopted from the French which one would like to see banished from our medical literature. As pointed out a few years ago by myself (1941) in dealing with the history of this affection, it has become a habit—a bad habit, copied by one author from another, in ignorance of its original significance—when referring to angular stomatitis, to give as a synonym this foreign word. It was first used by a French doctor named Lemaistre in 1886 as the title of an article—"De la perlèche: du streptococcus plicatilis." He described a condition—which closely resembles angular stomatitis—that he had observed to be common among children in the neighbourhood of Limoges,

where it had long been recognized by the inhabitants under the vulgar term "perlèche"—derived from the verb *lécher*, to lick, as it had been noticed that the sufferers had the habit of "feeling for" the sore place with the tip of the tongue. Lemaître believed the disease was due to a streptococcal infection and that it was contagious, as some 10 to 30% of school-children suffered from the complaint.

Subsequent authors, influenced by its supposedly streptococcal origin, used the word *perlèche* to denote an impetiginous affection of the corners of the mouth. If, therefore, *perlèche* were and be an impetiginous affection the word should not be used for a lesion due to hyporiboflavinosis. On the other hand, it seems to me very possible that the Limoges children were suffering from riboflavin deficiency, in which case the condition, defined as due to a streptococcus, was incorrectly described. In either case to retain the word is only to confuse the issue.

It is of interest in this connexion, however, to note that cultures prepared by Riddle, Spies, and Hudson (1940) from lesions at the angles of the mouth in cases of riboflavin deficiency yielded a pure growth of *Staph. aureus* in 80% and *Str. haemolyticus* in 20%, and that the organisms disappeared when the lesions healed with riboflavin therapy.

The angular stomatitis occurring in sprue appears to be due to riboflavin deficiency; some uncertainty still exists as to whether the similar condition seen in simple achlorhydric anaemia or idiopathic hypochromic anaemia and in that type presenting the Plummer-Vinson syndrome is due to the same cause. Some observers (Aykroyd, Smith and Martin, Rosenbaum and Jolliffe, Machella, Spies, etc.) have failed to obtain a satisfactory response to riboflavin therapy. I have met with similar cases, but it must not be forgotten that a considerable increase in dosage or administration by parenteral route may be necessary before an effect is obtained.

In regard to the glossitis, Sydenstricker and his colleagues have said: "The tongue is clean, the papillae flattened and mushroom-shaped and hypertrophic, the colour is definitely purplish red or magenta." This tongue is certainly characteristic, but whether of diagnostic value alone seems doubtful. By microscopy the filiform papillae are seen to have lost their keratinized tip, they are mushroomed out, swollen, and slightly oedematous, forming a pavement of semi-transparent hemispheres like minute jellyfish, while in the centre of each may be seen a dilated and distorted capillary loop, comparable to those mentioned as occurring elsewhere. Later, irregular patchy denudation may occur, giving rise to a condition which has been called "geographical tongue."

Ocular Manifestations

The ocular manifestations of hyporiboflavinosis have received a good deal of attention of recent years. Careful studies of the effects of deficiency states on the eyes of experimental animals began with the work of Wolbach and Howe (1925) upon vitamin A deficiency in the rat and the production of corneal vascularization, a condition resembling interstitial keratitis and cataract.

In 1939 Bessey and Wolbach published their work on vascularization of the cornea in riboflavin-deficient rats. In the same year Sydenstricker and his co-workers, after the original communications by Sebrell and Butler, described the symptomatology of "ariboflavinosis," but no mention was made of ocular signs and symptoms. The following year saw the first reference to eye lesions, and a more elaborate communication appeared on the subject by Sydenstricker and his colleagues. The objective signs described included injection of the bulbar and palpebral conjunctiva and of the fornix, circumcorneal injection, engorgement of the limbic plexus, and vascularization of the cornea; further, superficial opacities and deeper interstitial changes, sometimes diffuse, sometimes patchy, were noted, also congestion of the sclera and iris, and in some cases frank iritis. The authors concluded that "keratitis" is the principal ocular lesion of ariboflavinosis: the earliest and most common sign is circumcorneal injection.

The full realization of these lesions became possible only when slit-lamp microscopy was introduced for their study, a fact which probably explains their non-recognition in the older

syndrome, more especially as the subjects were all coloured peoples with very dark irides.

Apart from the symptoms referable to these conditions—"itching and burning sensations," "roughness of the eyes," and photophobia—the one subjective symptom in all these cases was impaired visual acuity, referred to as dimness of vision or partial blindness, associated with mydriasis.

Sydenstricker remarked: "Functional disturbances of vision out of all proportion to visible changes in the cornea were present in a number of patients with oral and lingual as well as ocular lesions of ariboflavinosis," but he offered no explanation. I think American observers have failed to realize the significance of the *subjective* symptoms as distinguished from the *objective* signs. All the congestive signs I look upon as part of the general capillary dysgergia, comparable to those in the skin but so situated as to be freely open to examination. On the other hand, the visual disturbances I believe to be due to a lesion in the nervous system with no immediate connexion with changes in the eye. That this should be so appears never to have occurred to any of those who have published their findings; that some condition akin to a retrobulbar neuritis would best explain the symptom has never been considered apparently by American observers. I shall refer to this question later.

There are other observations recorded from the United States and elsewhere which are based, I venture to think, on misconceptions in regard to the normal. In the article to which I have already referred mention is made of a "striking increase in the number of vessels composing the limbic plexus" and of replacement of "the normal narrow avascular zone between the limbic plexus and the sclero-corneal junction by a dense capillary network," etc. Elsewhere the statement is made: "For reasons not apparent arcus senilis would seem to offer some obstacle to the extension of the capillaries beyond the sclero-corneal junction."

This is not the place, perhaps, to discuss ophthalmological minutiae; but inaccuracies have already crept into the literature on the subject, as in H. Jegher's *Advances in Internal Medicine* (1942) and some of our own textbooks, and are in danger of being perpetuated, so that some reference must be made to them.

My own observations—and I speak with considerable experience, having, with my colleague Prof. Brunel Hawes, examined by slit-lamp microscopy the eyes of between four and five thousand individuals, aged from 3 to 93 years of age, healthy and sick, with and without ocular disease—lead me to believe that there is always a complete limbic plexus and there is no narrow avascular zone between the limbic plexus and the sclero-corneal junction as has been maintained by Kruse. Scleral digitations are outlined by capillary loops. There is never any increase in the number of vessels composing the limbic plexus. Vessels certainly do cross the arcus senilis.

Few authors appear to have recognized that in the limbic plexus they are dealing with a physiologically very active capillary bed, as was so ably demonstrated ten years ago by Basil Graves in his studies on the vascularization of the cornea, observations which seem to have escaped the notice of practically everyone who has written on riboflavin deficiency. It is really only a matter of the extent to which vessels are open or closed. I have found that in order to study this problem with advantage it is essential to determine the reactivity of the vessels in this area by the use of capillario-dilator and -constrictor drugs.

By such means—and, so far as I know, no one else interested in riboflavin deficiency has used the method—it is possible to demonstrate a complete limbic plexus, for example, in an old man whose limbus on first examination appears to be avascular. On the other hand, one can satisfy oneself that a completely constricted and empty capillary becomes invisible. The method also serves to demonstrate telangiectasis formation, etc.

In regard to the actual vascularization of the cornea, my own experience confirms that of some others who have carried out surveys (Youmans *et al.*, 1942; Wilson, 1941; Kodicek and Yudkin, 1942; Pett, 1943; Tisdall *et al.*, 1943; Wiehl and Kruse, 1941; Scarborough, 1942; Gregory, 1943; Sandstead, 1942; Machella and McDonald, 1943; Goldsmith, 1943; Keith Lyle

et al., 1944; Ferguson, 1944; Scott, 1944) in showing that it is not an unequivocal sign of ariboflavinosis; but that such a condition does not occur, as suggested by Vail and Ascher (1942), is incorrect. When these authors assert that—to use their own words—“Sydenstricker’s pictures as well as his descriptions suggest that what he termed corneal vascularization is nothing more than extensive engorgement of the pre-existing limbal meshwork except in cases of obvious corneal disease,” they display, I think, merely a lack of appreciation of the facts.

Another point I should like to make: my experience goes to show that it is quite impossible, owing to the great variability, to formulate any satisfactory method of notation for describing the degree of vascularity of the limbus and cornea, as has been attempted by some observers, including Keith Lyle and his colleagues (1944). No one seems to have commented on the individuality of the pattern of the intracorneal vascular network, which differs from that in vascularization associated with keratitis of inflammatory origin, etc. It is a point which may prove to have some significance.

Sydenstricker has drawn attention to the appearance of signs of ariboflavinosis in diabetes. The condition called rubeosis iridis—the subject of a communication by myself in 1942—its relationship to glaucoma, and the relationship of both to diabetes may here be mentioned.

As to the cause of the corneal vascularization, Bessey and Wolbach suggested it was of the nature of a compensatory process to bring blood into closer contact with the deeper layers of the corneal epithelium when the cornea is suffering from riboflavin deprivation. This explanation has been generally accepted in America and has found an adherent in Kruse, but to my mind it is no explanation at all and hardly consonant with Nature’s methods. It has been assumed that riboflavin exists as such in the cornea and that it reaches the cornea by diffusing from the limbic plexus. Again, it has been held that riboflavin in the cornea is destroyed by light, as it is known that the pure substance is converted into an inactive form by ultra-violet irradiation. I must confess it appears to me strange that Nature should provide the cornea with riboflavin, there to be destroyed by light.

The work of Philpot and Pirie (1943) on the eye of the ox probably points much nearer to the truth of what obtains in man. They found that all the riboflavin present in the ocular tissues is in its coenzymatic form, which is unchanged by sunlight. They give the following values in microgrammes per gramme weight: for the substantia propria of the cornea, 0.2; ocular conjunctiva and corneal epithelium, 2.0; retina, 4.0; and, be it noted, lacrimal gland, 6.5; Meibomian gland, expressed secretion, 4.0. These authors pose the very pertinent question, Is it “possible that the riboflavin of the corneal epithelium is obtained from the lacrimal secretions rather than from the blood of the limbal loops”? Personally I feel that such a possibility would best fit the facts.

It appears to have been generally assumed that vascularization of the cornea is part and parcel of the same process as limbic injection. For my part I believe that with the earliest trophic changes in the cornea, due to riboflavin deprivation owing to a deficiency in the lacrimal secretions, proliferation-promoting intercellular hormones—to use the term adopted by Loofbourow (1942) for substances released by intact cells, when submitted to damage, into the surrounding intercellular fluid—are formed which stimulate the loops of the limbic plexus to throw out new vessels.

It would also offer an explanation of the occurrence of corneal vascularization in the vitamin-A-deficient rat which appears to be similar to, if not identical with, that associated with riboflavin deficiency. While Bessey and Wolbach referred to a change in permeability of the corneal epithelium as possibly being an important factor in causing vascularization in vitamin A deficiency, they looked to an interference with corneal respiration, and did not visualize, apparently, the possibility of that same change in permeability denying to the cornea its supply of riboflavin. The supply itself might be deficient, too, as the result of changes in the lacrimal and other glands. It is suggested, therefore, that the corneal vascularization in vitamin A deficiency may be a manifestation of a local riboflavin deprivation.

Corneal vascularization has also been described as associated with the following conditions, but further study will be necessary before their respective relationships are settled: (a) “Some unidentified component of vitamin B complex” (György, Echart, and Johnson, *The Biological Action of Vitamins*). (b) Lysin and tryptophan deficiency (Trotter and Day, 1942; Albanese, Randall and Holt, 1942, 1943). (c) Zinc deficiency (Follis *et al.*, 1942). (d) Sodium deficiency (Follis *et al.*, 1942). (e) Thallium deficiency (Buschke, 1913).

Neurological Symptoms

To the syndrome under discussion I admitted a group of neurological symptoms, all on the sensory side, chief among which were a sense of muscular weakness, incoordination, ataxia, and paraesthesia—unassociated with any real loss of power, any loss of sensation, or any muscular wasting—together with loss of visual and auditory acuity.

Though in the past these symptoms have been referred to by some authors as due to a peripheral neuritis, possibly influenced by ideas associated with beriberi, they have in fact no relation to those of that disease; nor have they anything in common with the peripheral neuritis described among alcoholic pellagrins in the United States, where the latter condition seems to have completely overshadowed all other neurological manifestations.

While I have suggested that these neurological symptoms, as in the case of other parts of the syndrome, are due to a hyporiboflavinosis, there is the possibility that some other factor may also be involved.

These neurological symptoms are of the same order whether associated with pellagra or not. They may be recognized in the accounts given by Scott and by Strachan of the neuritis in Jamaica, by Fitzgerald Moore in West Africa, by Landor and Pallister in Malaya, etc.; but for a fuller description I am going to the case of an English child, whom I had under my care some ten years ago, suffering from an acute recurrence of pellagra, exhibiting symptoms which we should now refer severally to nicotinic acid and riboflavin deficiencies. This child—incidentally, the first case of pellagra in this country ever known to have recovered—I was able to watch constantly day by day during a period of observation and during treatment, which was with yeast and liver extract. Nicotinic acid and riboflavin were then unknown.

The symptoms were entirely on the sensory side; together they formed a complete picture of the “cerebellar syndrome”—as that term has been used in its wider sense to include muscular weakness (“cerebellar asthenia”), muscular hypotonia, ataxia, asynergia, astasia, dysmetria, dysidiadokokinesis—together with nystagmus, vertigo, tremor, typical gait, and characteristic “pendulum” knee-jerk. At the same time there was some apparent mental apathy, hyper-emotionalism, as shown by the ease with which the child was moved to laughter or tears; and a facies somewhat reminiscent of Parkinsonism. Visual and auditory acuity were not tested. The most striking point about these symptoms was their changing measure, with rapid oscillations towards improvement or the reverse, suggesting fluctuations in the exciting cause, a reversible disorder of function. I am going to suggest that the disorder is located in the capillary bed serving certain areas in the central nervous system and that the symptoms are the expression of a metabolic disturbance in nervous tissue produced by the capillary dysergia resulting from hyporiboflavinosis. All those impulses serving the subconscious synergic regulation of voluntary co-ordinated movements, after relay, reach the cerebellar cortex. To them should be added those coming from Deiters’s nucleus, the relay station of the vestibular nerve.

The cerebellar cortex is the receptive centre; co-ordination presumably takes place in the very rich synapse plexus of the molecular and granular layers; while the cerebellifugal fibres arise not in the cortex but from the intracerebellar nuclei, the chief of which is the dentate nucleus. On the other hand, after relay in the posterior horn, the fibres subserving skin sensation, pain, and temperature pass to the ventro-lateral nucleus of the thalamus. The thalamic nuclei are the centres for the correlation of sensory somatic impulses of all kinds before transmission to the cortex, whose activities probably enter into consciousness.

The initial reversible functional disorder, which of course if allowed to persist long enough leads to an irreversible lesion, is situated. I believe, in the synaptic structures of the cerebellum and is caused by a disturbance of its capillary blood supply. For the necessary facts I must turn to observations made on animals.

The metabolic activity of brain tissue is high; in the dog Craigie puts the oxygen consumption at 10% of the total for the whole body, whereas the brain weighs only 2% of the weight of the animal.

Capillarity of Nervous Tissues

The "capillarity"—that is to say, the relative number of capillaries in nervous tissues—varies very considerably in different areas and in different nervous-tissue elements. It is greatest in those areas and in those elements in which functional activity is greatest and metabolism highest. Those elements which have the greatest functional activity are the first to suffer the effects of any interference with their normal metabolic needs. As stated by Gasser (1937), the grey matter and the white matter of the central nervous system are differentiated by their metabolic needs. Greater vascularity, greater oxygen consumption, and greater susceptibility are characteristic of the centres as opposed to the fibres. This is not due, however, to the cellular content of the centres. The evidence goes to show that it is bound up with the mass of fine protoplasmic strands contributed by dendrites, terminal axon arborizations, and other synaptic structures, which together go to make up what Gasser refers to as the "neurophil"—a word which I think we would spell with a "y" instead of an "i," as it is presumably derived from the Greek *φύλη* = a clan.

For its proper functioning this system of fine strands of protoplasm demands a continuous expenditure of energy: lack of oxygen, etc., must soon bring about loss of function. In view of the fact that the surface area of a given volume of cytoplasm increases inversely as the diameter of the strands of which it is made up, it is obvious that the metabolism in the fine strands of neurophil must be much higher than that in the cell bodies and axons.

Dunning and Wolff (1937) estimated (in the cat) the relative surface of the nerve-cell bodies, excluding the neurophil, in relation to the length of capillaries per cubic millimetre, in the parietal cortex, the trigeminal ganglion, and the superior cervical ganglion, and showed that there was no correlation between the degree of vascularity and the cellular content of the grey matter. He inferred, therefore, that the correlation lay between the degree of vascularity and the neurophil.

The actual degree of capillarity in various parts of the nervous system has also been determined by Craigie (1919, 1938). The relative average vascularity of different regions in the central nervous system of the rat is given below in units, adapted from Craigie's figures. He showed that the number of capillaries in the grey matter is greater than in the white matter. The least vascular grey matter is still one and a half times richer than the white matter. The vascularity of sensory nuclei is greater than that of the motor nuclei.

(a) Postero-lateral column (Burdach)	10
(b) Antero-lateral descending tract	12
(c) Antero-lateral ascending tract	14
(d) Pyramidal tract	20
(e) Postero-mesial column (Goll)	24
(f) Substantia gelatinosa Rolandi	34
(g) VIIth C.N. motor nucleus	42
(h) XIIth C.N. nucleus	46
(i) Vth C.N. motor nucleus	46
(j) Ventral horn	52
(k) Vth spinal nerve nucleus	53
(l) Deiters's nucleus	54
(m) Cerebellar cortex, molecular layer	56
(n) Dorsal horn	58
(o) Inferior olive	59
(p) Superior olive	64
(q) Vth C.N. sensory nucleus	64
(r) Cerebellar cortex, granular layer	68
(s) Nucleus dentatus	72
(t) VIIIth C.N. vestibular nucleus	78
(u) VIIIth C.N. cochlear nucleus	84

The most highly vascularized area in this set of observations was the dorsal cochlear nucleus (84), which is twice that of the

facial motor nucleus (42) and eight times that of the fasciculus cuneatus (10). Nearly equal in vascularity to the cochlear nucleus comes the vestibular nucleus (78), followed by the dentate nucleus (72) and the granular layer of the cerebellar cortex (68). The relative position of the dorsal horn of the cord (58)—which includes Clarke's column—the molecular layer of the cerebellar cortex (56), and Deiters's nucleus (54) should also be remarked.

These figures for capillary vascularity appear to me most significant. They offer, I believe, the explanation of the localization of the group of the neurological symptoms that I have described. The cerebellar syndrome is due to a disorder of function of the cerebellar "neurophil" as a result of being a tissue with high capillarity. I have not been able to find figures for the thalamus, but a similar disturbance in the thalamus might account for the sensations of "burning pain" without causing loss of skin sensibility. The emotionalism might perhaps similarly be explained; while a widespread but early functional upset in the cortex might produce the Parkinson-like condition and mental dullness. The figure for layer II of the occipital cortex probably approximates to that of the cochlear nucleus, followed in descending proportion by the parietal, temporal, precentral, and insular cortex.

This distribution of functional disorders I shall again refer to when I come to consider such pathological evidence as there is, but here two points may be added.

Oxygen consumption of cats' brain, estimated by the tissue-slice method, was found to be about the same in the parietal cortex as in the cervical sympathetic ganglion but seven times that of the trigeminal ganglion—confirming the view that metabolic activity lies in the neurophil rather than in the cells. This correlation is also borne out by the work of E. Gordon Holmes (1930), who showed that the distribution of cytochrome and that of cytochrome oxidase run parallel to each other and to the rate of oxygen consumption.

The sites of the primarily functional lesion causing the loss of visual acuity and that causing loss of auditory acuity are uncertain, but I believe the lesions in the two conditions are of the same nature as elsewhere in the nervous system—i.e., a capillary dysergia. The high figure given for the capillarity of the cochlear nucleus is worthy of note, but there is none for the lateral geniculate body. Sydenstricker, who found the fundi normal, seems to suggest that the dimness of vision in his cases was due to the changes in the cornea; loss of auditory acuity he does not mention. It will be remembered, however, that Fitzgerald Moore also found a normal fundus in his early cases, but afterwards he ascribed the amblyopia to a retrobulbar neuritis as I had done, and of course later changes in the disk become obvious.

In the Spanish Civil War Grande Covian and Jimenez Garcia (1940) noted, among the syndromes they described, one which consisted of loss of visual and auditory acuity, commonly associated with the affection of the tongue and lips and neurological symptoms, including paraesthesiae and ataxia.

Impaired hearing was of course recorded by the older pellagrologists, as also were the ophthalmological conditions (Quaglino, Ferradas, Guaita, Denti, Rampoldi, Ottolenghi). During the present century really very few observations have been published (Whalley, 1909; Tucker, 1911; Ridlon, 1916; Calhoun, 1918; Jaensch, 1930; Krylov, 1932; Cronin, 1933; Levine, 1934; Carrol, 1936; Fine and Lachman, 1937; Laval, 1939; Mendoza Gonzales, 1941; Alessandri *et al.*, 1942).

I think the evidence, so far as it goes, supports the idea that the condition in pellagra is essentially the same as that met with apart from pellagra and included in the hyporiboflavinosis syndrome. I should prefer to call it a (retrobulbar) optic neuropathy.

The lack of systematization of the lesions in the central nervous system has generally been remarked (Kinnier Wilson, 1914; Greenfield and Holmes, 1939; Pauly and Deprecq, 1939), and remained unexplained up to date. There is a systematization, but it is one based on the neurophil.

Pathology

The post-mortem findings in riboflavin deficiency in animals are not very conclusive in regard to the nervous system, but

on the whole would seem to lend support to the views expressed above (Street and Cowgill, 1939; Zimmerman, Cowgill, and Fox, 1937; Page, 1937; Wintrobe, Mitchell, and Kolb, 1938; Phillips and Engel, 1939).

There is no certainty concerning the pathological changes in the viscera in man in nicotinic acid and riboflavin deficiencies. It is just worth remembering, however, that degenerative changes occur in the heart muscle in pellagra, that the liver always shows fatty changes, most marked perhaps in infantile pellagra, while in the dog "yellow liver" is characteristic of ariboflavinosis. Scott mentions myocardial changes "with dilatation and congestion of the cardiac capillaries," and an angioma-like condition in the heart.

There is, so far as I know, no account of the post-mortem findings in human riboflavin deficiency. No case of "aribo-flavinosis" has come to necropsy in America. None of the cases described by Fitzgerald Moore and by Landon and Pallister found its way to the pathologist. I have therefore turned to the detailed pathological records by Scott upon two cases of the Jamaican disease which he called "central neuritis" but which I have ventured to suggest, in the light of present-day knowledge, may have been acute hyporiboflavinosis. I wondered whether one would find a pathological picture in the central nervous system with irreversible tissue changes, such as might be expected to follow the early reversible functional disorder that I have supposed to occur. It is not possible to deal with these here in detail, but I believe Scott's findings support my thesis.

Scott noted the many points of resemblance between his own findings and those of Singer and Pollock (1913) in pellagra, who in turn had stated that the histopathological picture in pellagra was identical with that described by Adolf Meyer (1901) as "central neuritis." This condition, later referred to by Pearson (1920), I have little hesitation in suggesting is the later stage of the functional disorder I have described. It starts, I believe, in the neurophyl as the result of the capillary dysgergia, and spreads to the cell, to be followed by changes in the axone.

The changes found in the pseudo-encephalitis of Wernicke associated with vitamin B₁ deficiency, consisting of capillary dilatation in certain areas of the nervous system—viz., the paraventricular grey matter of the third ventricle, the mammillary bodies, the peri-aqueductal region, the corpora quadrigemina, and the floor of the fourth ventricle—make an interesting comparison.

If, as I have suggested, riboflavin deficiency interferes with the normal functioning of the capillary, with the production of a tissue anoxia, it would seem of interest to compare the nervous symptoms so produced with those referable to the nervous system in chronic carbon monoxide poisoning.

C. K. Drinker in his monograph upon the subject states that headache occurs in 74%, dizziness in 50%, burning of the eyes in 32%, gastro-intestinal disturbances in 24%, drowsiness in 28%, cardiac disturbances in 18%, insomnia in 20%, faintness in 12%, neurological and mental symptoms in 17%. Among the last-named are giddiness, nervousness, emotionalism, tremors, muscular weakness, increased reflexes, neuromuscular pain, sensations of numbness and chilliness, paraesthesiae, ataxia, muscular incoordination, disorders of vision and hearing, neurotic and psychotic manifestations.

The general resemblance of these symptoms to those I have described in the syndrome here dealt with is, I think, worthy of note, especially when it is remembered that carbon monoxide and cyanide are believed to operate by inactivating cytochrome oxidase and thereby inhibiting oxygen consumption by preventing electron transfer—cyanide by uniting with the iron when in the "ferric" form, carbon monoxide when in the ferrous form. Of cyanide I shall not speak, but I might mention here that Quastel (1943) has recently analysed the evidence concerning the inhibition of oxygen uptake by narcotics, and concludes that flavoprotein is the sensitive factor.

Summary

An attempt has been made to disengage from the clinical affection we call pellagra a group of symptoms which may also be met with

as a more or less complete syndrome apart from those symptoms generally recognized as due to a nicotinic acid deficiency.

This syndrome includes a good deal more than that to which American authors have given the name "ariboflavinosis." Any differences are, however, I think, a question of the comparative intensity and duration of the underlying pathogenic process.

I have considered the whole syndrome, for the sake of convenience, as due to riboflavin deficiency—a hypo-riboflavinosis I should prefer to call it rather than an a-riboflavinosis—but some uncertainty must still exist as to whether any other factor in the B₂ complex plays a part.

All the symptoms of the syndrome respond to treatment with yeast. It is suggested, in the absence of any knowledge on the subject, that we are warranted in making the assumption that the cells forming the capillary endothelium require all those elements needed by other cells in the body for their normal metabolism—sugar, oxygen, etc., including riboflavin.

It is further suggested that the first tissue to suffer the effects of riboflavin deficiency is the endothelium of the capillary system; that the initial result is a reversible functional disturbance of the capillaries—a "capillary dysgergia"—which at the present time cannot be more accurately defined, but which is manifested by dilatation of these vessels and impaired flow; that in turn there is an interference with the normal cellular metabolism and in consequence a derangement of tissue function by disturbance in the *milieu intérieur*; and that the derangement of tissue function is relatively greatest in those tissues which possess the highest degree of capillarity and whose metabolism is greatest.

So long as the intensity of the functional disorder be not too great and so long as it do not persist too much, complete recovery may take place, otherwise irreversible processes occur which lead to pathological changes.

The hypothesis put forward would appear to offer an explanation of the incidence of symptoms and distribution of signs in riboflavin deficiency.

The interference with tissue-cell metabolism is probably of the nature of an anoxia in its wide sense.

It is suggested that disorders of capillary function—"dysgergia"—quite apart from affections of the rest of the vascular system, may play a much more important part than has commonly been supposed in the pathogenesis of many conditions, including pellagra due to nicotinic acid deficiency.

At the risk of appearing mono-ideistic, I cannot help feeling there is perhaps a wide field awaiting investigation along such lines—a field embracing such widely separated conditions as fibrositic rheumatism, some psychoses, and neuropathies.

POST-OPERATIONAL STRAIN IN THE NAVY

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The concept of an operational strain syndrome is open to criticism on a variety of grounds. There is, for example, little evidence that psychiatric breakdowns associated with operational stress differ symptomatically from those that are not. Moreover, not all reactions supposedly associated with operational stress are due to it, and in wartime there is a very real danger of over-emphasizing the dramatic, such as exposure to enemy action, when less dramatic events, such as the regimentation and frustration of Service life, separation from home, and domestic difficulties, may really possess more significance. Again, the conception of an operational strain syndrome runs the grave risk of creating an honourable as opposed to a dishonourable or at least less honourable category.

There is, however, yet another objection, to which curiously little attention seems to have been paid—namely, that the concept is descriptively misleading in that most men break down after, rather than during, a period of stress; and it is with the phenomenon of post-operational strain that this paper is mainly concerned.