VITAMIN B_2 AND PELLAGRA

THE ETIOLOGY OF PELLAGRA

BY

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The purpose of this article is to direct attention to the fact that, though Goldberger's researches have thrown very considerable light on the question of the etiology of pellagra, there are several points in this problem which are still obscure. The earlier theory that pellagra was caused by a deficiency of protein of good biological value was discarded by Goldberger after a series of researches, in which he found that, while caseinogen provided little relief, certain materials like brewer's yeast and fresh meat afforded both protection and cure.[1 2] Convincing evidence was advanced by Goldberger and Lillie,[3] who produced a pathological condition in rats by giving them an alcoholic extract of corn-meal, which is known to be rich in the so-called antineuritic factor, as the sole source of water-soluble B. This condition was characterized by a failure of growth, loss of fur, and buccal lesions, and was considered to be the experimental analogue of human pellagra. Inclusion of yeast, in which the antineuritic substance was almost completely destroyed by autoclaving, cured and prevented all these symptoms. These experiments, confirmed by others,[4] have led to the general belief that the water-soluble B of McCollum consists of a relatively heat-labile factor which is specific for polyneuritis and a more thermostable constituent (Goldberger's P-P factor) which is concerned in the prevention and cure of pellagra. These two factors have now been respectively designated as vitamins B_1 and B_2 in this country.

ETIOLOGICAL CONSIDERATIONS

In spite of the above work, however, it is not yet clear whether pellagra, experimental or human, is the result of an uncomplicated deficiency of the factor called vitamin B_2—that is, the substance which supplements a purified preparation of vitamin B_1 for the development of vitamin B deficient rats. Nor is it certain that the dermatitis condition in rats is a perfect analogue of human pellagra. This condition in rats cannot be produced uniformly by the deficiency of vitamin B_2 in the diet. Attention is drawn to statements in the literature[5 6] that pellagra symptoms in rats may be produced when they are still growing, while, very often, the arrest of growth in vitamin B_2 deficiency is not associated with any skin symptoms. Elsewhere[7] I have described a curious kind of depilation in rats subsisting on a vitamin B_2 deficient diet, in which the fur fell off not in patches, but uniformly. This occurred fairly regularly when young animals were kept on a vitamin B_2 deficient diet with only occasional administrations of small doses of vitamin B_2, such that the deprivation of vitamin B_2 was not complete, but sufficiently severe to cause the weight of the animals to remain between 60 and 80 grams over a period of ten to twelve weeks. Lesions on the mouth and paws occurred only in a minor proportion of these animals. The symptom of depilation was rapidly cured by administration of Eli Lilly's liver extract No. 343. Leader[5] has recorded that small doses of marmite, sufficient to prevent beri-beri, are actually helpful in the production of pellagra-like symptoms in rats, an observation which is supported by the work of Sure and Smith.[6] It has been pointed out by Aykroyd[8] that rice, millet, and maize are all poor sources of vitamin B_2 as tested on rats, while human pellagra appears to be associated chiefly with the consumption of maize.

Bliss[9] has recently put forward the view that human pellagra, as well as experimental pellagra in rats and black tongue in dogs, is caused by iron deficiency. In a more recent paper[10] he has adduced fresh evidence in support of his claims. He observed depilation occurring in rats on an iron-deficient diet containing ample vitamin B; according to Elvehjem and Peterson,[11] hair is the richest source of iron in the body. The depilation of our rats on a vitamin B_2 deficient diet cannot, however, be due to a simple iron deficiency, as the food intake and, therefore, the iron intake was still sufficiently large to cover the iron requirements of the animal. This condition of depilation was not remedied, nor did growth resume on feeding 25 mg. of haemin per day. The haemin was dissolved in 0.2 *N* NaOH and precipitated in a finely divided condition by 0.2 *N* HCl, this suspension being fed in various doses. The dose fed was much in excess of that which could be absorbed by the animals, as was shown by a considerable excretion of haematin, indicated by the benzidine test. Nor did the condition improve on feeding 0.5 gram of haemoglobin per day. However, the experiments with haemin may have been complicated by an insufficient absorption from the gut, and hence they cannot be strictly compared with those of Kollath,[15] who states that the feeding of alkaline haematin prevents the appearance of pellagra symptoms in rats on a diet deficient in vitamin B. The fact that vitamin B_2 in certain preparations can be inactivated by autoclaving in an alkaline medium[12] argues against the proposition that vitamin B_2 deficiency is simply an iron deficiency. The possibility, however, must be recognized that pellagra, both clinical and experimental, might be associated with a disturbance in iron metabolism. The observation[5] that the presence of sugar in the diet causes pellagra symptoms to appear more regularly in rats may have some significance in this connexion, as Whipple, Hooper, and Robscheit[13] observed that the fasting anaemic dog was able to regenerate red cells and haemoglobin more readily than the animal fed with sugar. Sure, Kik, and Smith[14] have observed a distinct lowering of the red blood cell count in vitamin B_2 deficiency, and we have also observed the same in this laboratory.

COMMENTARY

The statement that clinical and experimental pellagra is the result of a simple deficiency of the dietary factor, vitamin B_2, has passed into current literature. The above analysis of the existing evidence indicates, however, the inadequacy of this assumption. On the other hand, the suggestion that pellagra is caused by a simple iron deficiency in the diet appears to be untenable in view of Goldberger's and of our own experiments. It is considered probable that pellagra is a complex syndrome arising from an association of various factors, in which the deficiency of an antipellagra factor (Goldberger's P-P factor), which is possibly, but not necessarily, identical with the growth-promoting vitamin B_2, is the main but not the sole factor. Thus, iron might be one of the limiting factors, especially so far as depilation is concerned. Preliminary experiments, carried out in conjunction with L. Mapson, indicate that a balance between vitamin B_2 and other dietary factors might be involved in this question, and that vitamin B_2 may play a part in a particular phase of iron metabolism.

Finally, it is considered that, instead of presuming the identity of the two factors involved in the definition[8] of vitamin B_2 as the "factor in the vitamin B complex other than the antineuritic, which promotes growth and prevents dermatitis in rats," the terms vitamin B_2 and antidermatitis (antipellagra ?) factor should not be used interchangeably, as has been hitherto the practice. Though the terms vitamin B_1 and vitamin B_2 might appear to

indicate some relationship between the two, it may be mentioned that so far they appear to be both chemically[12] and physiologically unlike.

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MÉNIÈRE'S DISEASE*

BY

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HARROGATE

For many years it was taken for granted that Ménière's disease was due to haemorrhage into the labyrinth. This misconception was due to a faulty reading of Ménière's original paper, in which there is no mention of this condition. He described the material found in the labyrinth of his well-known case as being composed of reddish plastic lymph. Alexander of Vienna considers that Ménière's patient suffered from leukaemia complicated by a leukaemic haemorrhage into the labyrinth. Escat thought that Ménière's disease occurred only in arterio-sclerotics, and ascribed the paroxysmal attacks to an intermittent spasm of the internal auditory artery, and the apoplectiform attacks to haemorrhage.

The exclusion of labyrinthine haemorrhage as an etiological factor placed this disease in a less formidable light, for haemorrhage from one intracranial blood vessel implies the possibility of haemorrhage from another, secondary to arterio-sclerosis and high blood pressure. But haemorrhages, arterio-sclerosis, and high blood pressure are absent in Ménière's disease. The vertigo due to spasm of the cerebral arteries in patients with arterio-sclerosis must be distinguished from the vertigo of Ménière's disease in which tinnitus and deafness are prominent symptoms.

INTRACRANIAL CAUSES

The rejection of haemorrhage and arterio-sclerosis as causes of this disease was followed by many theories and, naturally, by as many treatments. Thornval, a recent writer, considers that the main disturbance is in the medulla oblongata. Charcot (1874) and Dandy (1928) put forward the view that there was a lesion of the auditory nerve and not of the semicircular canals. Charcot recommended division of the nerve, and Dandy divided the nerve in nine cases with a resulting cure. Aboulker thinks that the syndrome is due to pressure on the nerve from a collection of fluid around it—that is to say, to an encysted meningitis or hypertension of cerebrospinal fluid in the lateral cisterna. He consequently does a decompressive trephine behind the mastoid, with or without incision of the meninges. Babinski, and, later, Blake, must have had the same idea, as they treated their patients by lumbar puncture. Quix also believes that this disease is due to intracranial hypertension, which acts on the otoliths via the ductus endolymphaticus instead of on the nerves. Kobrak also subscribes to this theory of an intracranial origin. According to his view the trouble is localized behind the labyrinth mainly in the cisterna pontis, and the increased pressure is transferred to the labyrinth via the porus acusticus or saccus endolymphaticus. He thinks that the excess of fluid is caused by an irritation of the choroid plexus or is due to a transudation resembling a circumscribed oedema of the skin. Kobrak uses atropine, pilocarpine, and adrenaline in examining his patients to find out whether the syndrome is associated with a vagotonic or sympathetico-tonic condition.

INTRA-AURAL CAUSES

The other theories to be considered all agree that the origin is intra-aural rather than intracranial. Thus Witmaack is of the opinion that toxins produced by a catarrhal condition of the middle ear diffuse into the labyrinth via the windows, and so produce an intra-labyrinthine hypertension. Quincke believes that the symptoms are due to an angioneurotic oedema of the labyrinth, which brings about an increase in tension of the endolymph. According to Portmann the hypertension originates in the labyrinthine blood vessels. He calls this hypertension of the labyrinth "glaucoma of the labyrinth," and considers that Ménière's syndrome is closely connected with vasomotor phenomena, and hence with sympathetic equilibrium. He believes that the vertigo is caused by a vaso-constriction of the blood vessels of the labyrinth, while tinnitus and deafness are produced by vaso-constriction of the vessels of the cochlea. This vaso-constriction elsewhere would produce pain, as in frostbite or Raynaud's disease. The sign of labyrinth disturbance is vertigo, just as the sign of a diseased cochlea is tinnitus. This vaso-constriction disappears after a sympathectomy, the consequence of which is a vaso-dilatation of the blood vessels of the labyrinth. He also considers that the constriction of the blood vessels may be caused by adrenaline. Portmann does not know whether the vascular stasis produced by vaso-constriction acts directly on he nerves or, as the result of an increase of pressure, on the semicircular canals. With the idea that vertigo was due to an increase of pressure in the semicircular canals he opened the saccus endolymphaticus after performing a mastoid operation without opening the antrum. On the supposition that vertigo was purely a vasomotor reaction he performed a perivascular sympathectomy on the common and internal carotid arteries, and injected drugs which inhibited the sympathetic system, attempting to cause peripheral vaso-dilatation by hot baths. Halphen, on the same grounds, applied cocaine (Bonain's solution) to the sphenopalatine ganglion, and stated that this led to the disappearance of the vertigo after an hour or two, due, presumably, to the inhibition of the sympathetic system. Lermoyez recommended liquor trinitrini in cases of suspected spasm of the internal auditory artery. Amyl nitrite and benzyl benzoate have also been recommended. Muck agrees with Portmann in that he has found his vaso-constrictor nasal reflex present in Ménière's disease. This indicates, according to Muck, the presence of an angiospastic condition of the auditory artery. He has successfully treated five patients with a meatless diet.

FAULTY WATER METABOLISM

Finally, Dida Dederding and Dr. Mygind of Denmark have originated a theory which solves all these problems. They definitely state that the symptoms of Ménière's disease are due to increase of pressure in the semicircular canals, which produces vertigo and deafness by displacement of the stapes. They attribute this increased

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