THE INFLUENCE OF THE TROPICAL ANEMIAS ON THE PHYSIOPATHOLOGY OF THE BRAIN *

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The tropical anemias subject to this study are the secondary ones so common to the tropics, and are directly traceable to ankylostomiasis, malaria and nutritional disorders. The latter diseases may occur by themselves, or else as aggravating factors to the other two types. Nutritional disorders do such damage, especially in ankylostomiasis, that it is hard to draw a nice distinction between these two contributing factors to anemia [1].

For this reason, and because it is difficult in the clinic, and even in the autopsy room, to specify exactly in conditions of anemia how much is due to ankylostomiasis, malaria or nutritional diseases, we refer collectively to "agents of tropical anemia" in their relation to cerebral physiopathology, even when we are endeavoring to make an anatomical analysis of their respective effects.

Any doctor with experience in tropical medicine—especially he who has worked in psychiatric institutions in the tropics—has noted the etiological influence of tropical anemias on certain psychopathic disorders. The cerebral lesions caused by the malarial parasite are well known, in contrast to the rudimentary knowledge of cerebral disturbances produced by ankylostoma anemia, which might also afford a physiopathological explanation of certain mental and nervous disturbances.

Recognized authors in tropical medicine call attention to the desirability of more intensive anatomical investigations for the clearer interpretation of these psychopathic conditions.

For correct interpretation of this problem it is hardly necessary to say that caution must be exercised in attributing

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psychopathic etiological influences wholesale to tropical anemias—no matter how frequently they are met with—for these anemias may exert only a secondary etiological influence. There are times, however, when the anemia indeed acts as the principal factor in the pathogenesis of endogenous psychoses. Also it must be remembered that mental disturbances due to definite dietary deficiencies (as pellagra and beri-beri) can be aggravated by ankylostomiasis, producing typical nervous and psychic symptoms.

Nevertheless, there are cases of ankylostomiasis in which the anemia and the lesions consequent to it are definitely the cause of the nervous disturbances, which are at times seen in this disease. Strong and Smillie [2] in the United States and Waite and Neilson [3] in Australia, have determined that retarded mental development in ankylostoma-infested children goes hand in hand with retarded physical development, which, however, generally becomes compensated with adolescence. There are more serious cases, however, where the mental disturbances which must apparently have an anatomical basis for their development, result in mental defectives "who may never entirely recover", to quote Strong. The well-founded opinions of these investigators led us to believe that in severe cases of tropical anemia cerebral lesions might exist, which belief we then substantiated in two autopsies. These pathologic findings might explain the physiopathology of persistent mental disorders.

One of these cases, a woman of 31 years, died of ankylostoma anemia with thrombosis, after premature childbirth. In ten different convolutions of the frontal and parietal lobes we found foci, each about the size of a kidney bean, which caused identifiable circumscribed indurations. On palpation, these nodules proved to be of a firmer consistency than the normal nerve tissue, and their surfaces felt like wrinkled, rough cloth. On section it was noticed that the cortical substance had disappeared to such an extent that the white substance extended to the surface of the brain. Histologically we found that the ganglion cells had disappeared almost entirely, being replaced by a gliomatous proliferation.

Interesting as these lesions appeared to be, we did not yet dare to connect them with ankylostoma anemia, but when we found a second case a short while after, we began to presuppose etiological relationship. In a child of six years who had died from ankylostoma anemia with marked evidences of dropsical affection, we found in the left mid-frontal convolution a focus exactly like those of the former case.

To make the histological description more comprehensible to the reader, we refer him to figure 1. Here we see, at the left (*a*) a section of the right mid-frontal convolution, in which are apparent the ganglion cells in regular and normal distribution. This contrasts with the figure at the right (*b*), which shows the focus mentioned in the homologous left region, and from which the greater part of the ganglion cells have disappeared, only a few remaining in the pyramidal zone, and already in process of disintegration. In contrast to this, the number of glial nuclei in this region is increased. When we consider a child, six years old who shows no signs of other diseases either on clinical examination, in family history or at autopsy, it is only reasonable to suppose with a good deal of foundation that the lesions have intimate relationship with ankylostoma anemia, more especially when we consider that the degenerated ganglion cells, which had disappeared entirely in the first case, proved the process to be of recent formation and progressing in a typical case of ankylostomiasis.

In reviewing the clinical histories of these two cases, no data were found regarding mental deficiency, probably because the immediate physical condition of the patients was so serious that it was deemed undesirable, or even useless, to put such questions to them as would disclose mental disturbances.

Our knowledge of the pathogenesis of the lesions gleaned from experimental observation of the migration of larvae through nervous tissue in laboratory animals, makes a logical base for the supposition that in our two cases the ankylostoma infection may have had a similar influence. Also, it is very probable that circumscribed states of cerebral anemia so fre-

quent in advanced ankylostomiasis might affect the ganglion cells, which are known to be sensitive even to temporary deficiencies of the supply of oxygen, to such a degree that complete anatomical restoration would be impossible. This hypothesis will appear at first sight to be at variance with the localization of the lesions limited to the convolutions, but one must take into account that the amount of blood which nourishes the different cerebral regions is continuously varying, following a functional rhythm which depends on the vascular innervation. Perhaps a more detailed histological examination would show us other lesions of the ganglion cells, a study hitherto impossible owing to the lack of necessary laboratory equipment, which defect we hope soon to remedy and advance our investigations.

Besides the mental defects that possibly result from the anatomical lesions already described, one also finds in cases of ankylostoma anemia acute nervous and psychic symptoms —real cases of dementia, severe enough to necessitate removal of the patients to the asylum, if they had not been sent there in the first place.

Apart from relatively rare cases of hemorrhage and softening of the brain determined by paradoxical embolisms, autopsy of ankylostoma cases very often shows extensive thrombosis of the cerebral sinuses, especially of the superior longitudinal, a process which continues into the pial veins, occasioning at times major hemorrhages in the cortical substance of the brain. In the investigation mentioned before [1], discussed before the Third Medical Congress of Panama, we called attention to the frequency of thrombosis in ankylostomiasis, noting that it was evident in 10 per cent of our autopsies of cases of this disease, the percentage rising to 15 in deaths under fifteen years.

Without quoting in detail the reference above [1], we will relate an observation we made recently in a child of five years who, in a state of profound prostration, died from thrombosis caused by ankylostomiasis. Autopsy revealed thrombosis of the transverse, oblique, straight and superior longitudinal sinuses, which extended to the pial veins as far

as the frontal lobes, causing extensive subpial hemorrhages, as is shown in figure 2. In the horizontal section of the brain may be seen the anterior poles, destroyed by extensive hemorrhages which extend posteriorly into the white matter (figs. 3 and 4). Microscopically we can see that the thrombosis of the pial veins extends to the intracerebral, causing perivascular hemorrhages, some distributed in circular formation, others in irregular, as can be seen in figure 5.

It is not surprising that intense nervous symptoms were absent in this case, as the patient was in a comatose condition, and also the lesions were located in the frontal lobes, which constitute in cerebral physiology the "silent zones".

Our explanation [1] of the high frequency of thrombosis (which explanation seems to agree with clinical observation), is that it is not only the hematological changes of anemia which occasion thrombosis, but probably also the changes in metabolism of the fluids, caused in their turn by the deficiency in nutrition common to the tropics, and which helps to create what we call a "hydropic constitution", which, damaging the barrier between the vascular system and the tissues, may favour the onset of thrombosis.

Having reviewed ankylostomiasis and nutritional deficiencies as factors of anemia in producing cerebral lesions, we wish to refer to malaria which operates in a similar manner to the two former factors, interfering with the proper functioning of this barrier. Cerebral lesions due to malaria have attracted attention, but not attention worthy of the gravity of the subject, nor have they been analyzed from the point of view which we are trying to present in this paper.

The abundance of pathological material which our Hospital offers has permitted us to study cerebral lesions, which we meet with frequently and which we shall illustrate in a series of microphotographs. In figure 6 is seen a cerebral vein of medium dimensions, which, in part, maintains its normal histological structure, but which in the remainder of its circumference presents a homogeneous appearance due to infiltration of the wall with blood plasma, obscuring its limits with the coagulated plasma contained within the

lumen. This anatomic lesion clearly shows that the barrier between the blood plasma and the wall of the blood vessel has been damaged.

Furthermore, one sees in paludism that the plasma which infiltrates the blood vascular walls frequently becomes impregnated with calcium. Figure 7 shows partial calcification in some sections of the blood vessel. In figure 8 the calcification is complete, involving principally the elastic fibers. In the final stages of calcification, the blood vascular walls are replaced by a rigid tube of calcium (fig. 9).

These lesions, which are not characteristic of malaria in older patients, we have found in young people of as low an age as six years, and in whom all factors except malaria could be excluded as an etiological cause.

There are occasions in which the transudation of plasma is not limited to the blood vascular walls, but also permeates the perivascular tissue. Figure 10 shows the homogenization of the wall and, further off, a round homogeneous body which is stained with haematoxylin, and which presents the characteristics of the corpora amylacea which are found in numerous degenerative processes of the nervous system. These probably result from precipitations of albuminoid substances surrounding granulations of various natures, and this may indicate an infiltration of cerebral tissue with blood plasma; or, in other terms, the breaking down of the barrier between the blood vascular system and the tissues. Figure 11 shows a similar process, in which is seen homogenization of the blood vascular wall, and as indication of the progressive plasma infiltration, various corpora amylacea irregularly distributed in the cerebral substance. These can exist in great numbers, clustered around the veins and arteries as is shown in figure 12, in which they appear to be in the adventitia of the vessels.

The changes of the cerebral blood vessels in malaria also occur in the leptomeninges by a similar process of disintegration. In figure 13 we see a large number of corpora amylacea in the subpial zone of the brain as a consequence of infiltration of plasma through the pia mater.

In some cases the cerebral lesions due to malaria are somewhat different. Figure 14 shows masses precipitated round a blood vessel, which can be differentiated from the corpora amylacea by their distribution and larger content of calcium. In the pathogenesis of these calcareous bodies one can see the same factor of altered metabolism previously alluded to. These calcareous bodies can be so numerous (fig. 15) that extensive blood vascular regions are transformed into calcified masses.

Because of its clinical importance in the correct interpretation of certain convulsive and comatose conditions due to paludism, we must add that some processes, like those mentioned, occur also in the pachymeninx. Anatomically, internal hemorrhagic pachymeningitis is the manifestation of blood vascular change which allows the passage of plasma, erythrocytes and fibrin through its walls to be precipitated on the internal surface of the dura mater, forming a thin membrane. This important anatomical pathologic lesion is found in 37 per cent of our cases of malaria, and only exists in about 5 per cent of the cases of ankylostomiasis without thrombosis.

The internal hemorrhagic pachymeningitis of paludism is sometimes followed by extensive subdural hemorrhages, due to rupture of newly formed capillaries during the organization of the pachymeningitic membrane. We have an exceptional case of extensive hemorrhage in which the accumulation of blood amounted to 1.5 cm. in diameter (fig. 16).

There is no doubt, then, that in the blood vascular changes of the brain and the meninges in paludism, the toxic and mechanical action of the parasites plays an important rôle.

These changes are doubtless produced in other blood vascular regions of the body, and are more difficult to confirm by reason of an obscure anatomic position.

As a summary of what we have related, we may say that the factors leading to the anemias such as those of ankylostomiasis, nutritional disorders or malaria may provoke the development of a hydropic constitution which in turn brings about changes of the blood and anatomical alterations, pro-

ducing a breaking down of the hematoencephalic barrier, which predisposes to thrombosis, as happens in ankylostomiasis, or in plasmic infiltration as in malaria. When these changes take place in the blood vascular regions of the brain, anatomic alterations ensue which afford a physiopathologic explanation of certain mental and nervous disorders which are observed in all clinics at which sufferers from anemias of the tropics present themselves.

Trans. E.K.

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