HISTOLOGIC EVIDENCE OF THE PATH OF INVASION OF THE BRAIN IN GENERAL PARESIS

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A topographic survey of the brain in cases of general paresis shows that, in the majority of cases, the brunt of the attack is borne by the frontal pole and the anterior parts of the convexity, while the occipital pole is relatively free. In 1913, the writer made a comparative histologic study of six areas from each hemicerebrum of the brains of fifty cases of paresis and found that the areas of most severe involvement, in the majority of cases, were those supplied by branches of the internal carotid artery. In a smaller number of cases the lesions were widespread and of about equal severity. Cases have been recorded with the maximum damage in the occipital region, that is, the area of distribution of the basilar system and with little or no involvement of the anterior portions of the brain. Apparently in the majority of cases the lesions are more or less strictly confined to areas served by the carotid system; in very rare cases, to that supplied by branches of the basilar artery, while in a considerable number both zones are involved.

HISTOPATHOLOGIC APPEARANCES

Paresis is one of the few mental diseases in which the diagnosis can be confirmed by histopathologic examination, and it is by means of this examination only that the diagnosis can be established with sufficient accuracy for careful scientific analysis. The criterion on which such diagnosis rests is not the destruction of the brain parenchyma, but the widespread perivascular accumulations of lymphocytes and plasma cells. The parenchymal changes are often severe, but they are not pathognomonic, and most typical cases of paresis will show areas of advanced vascular lesions with little or no demonstrable damage to the essential nerve tissues, while in very early cases the amount of damage to the brain structures may be very slight in comparison to the degree of perivascular infiltration.

These two points: (1) That the distribution of the lesions follows roughly one or the other or sometimes both of the main cerebral vascular stems, and (2) that the perivascular changes within the brain are at least as widespread as the parenchymal damage and frequently more so, has led to the conclusion that the path of invasion by the spirochetes is along the perivascular lymphatic channels and the meso-

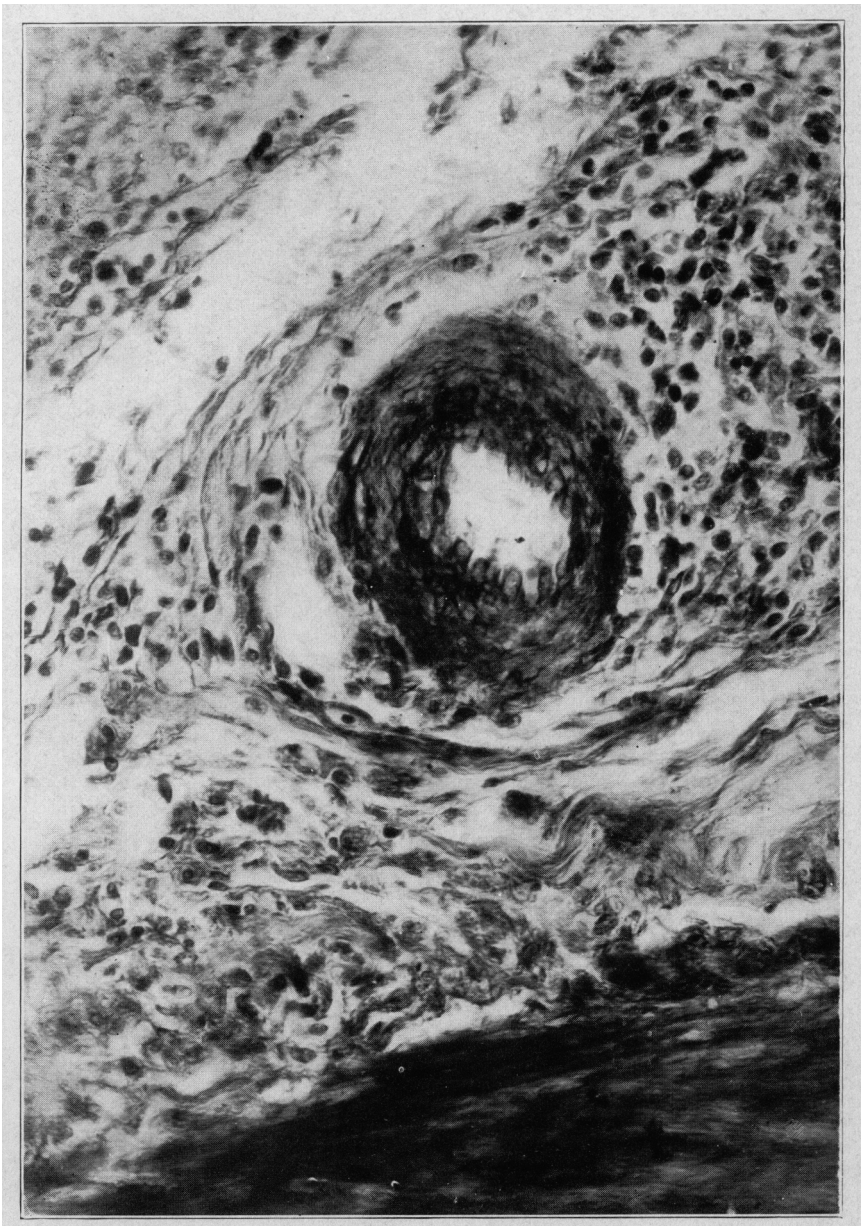
dermal tissues of the perivascular spaces — that is, that general paresis is essentially a perivasculitis with focal invasive spread to the brain parenchyma. This has suggested observations on the larger cranial vessels before they enter the brain mass, and material from nine cases of paresis has been studied with this point in view. The material in some cases was taken from the intracranial but extracerebral portions of the carotid and basilar arteries and in some from the carotids in the neck.

CHARACTER OF THE LESIONS

The lesions encountered naturally fall into two groups: (1) those in which the process is evidently stationary, and (2) those showing evidence of progressive chronic inflammation. The stationary lesions are comparable in every respect to those of healed syphilitic endarteritis. The endothelium is intact, but between it and the elastica is in many places a fairly thick mat of loose-meshed but very well preserved connective tissue which marks the site of earlier endothelial proliferation. The elastica often shows the fibrillation which occurs in syphilitic arteritis, and not infrequently there is a suggestion of the formation of new elastic laminae in the connective tissue scar. These lesions agree with the criteria usually accepted as differentiating syphilitic vascular disease from the other types of arteriosclerosis — that is, splitting of the elastic lamina with separation of the intima and media by a connective tissue scar in which the cell and fiber elements are well preserved and which shows little or no alterations of a degenerative character.

It must be borne in mind that these lesions, while corresponding nicely with those of healed cases of arteritis of established syphilitic origin, do not in themselves offer definite proof of their own etiology. Lesions of this type were found in varying grade in eight cases of the series of nine, and with the known syphilitic infection of all paretics I think it fair to conclude that these patients had suffered with varying degrees of syphilitic arteritis of the cranial vessels during the earlier stages of the syphilitic infection.

The active chronic inflammatory lesions consist in a lymphocyte and plasma cell exudate in the perivascular connective tissue sheath — the adventitia — which is quite comparable with that of the vessels within the brain substance, although the plasma cells are a little less numerous and apparently do not tend to mass together into the mosaics seen around many smaller arterioles in the cortex. Such exudates were observed in eight of the nine cases. In one case, in addition to this cellular infiltration, one very small vessel traveling in the adventitia of the carotid in the neck showed the reduplicated succulent swollen endothelial cells which are found in the acute stages of syphilitic endarteritis as shown in the accompanying illustration.



The heavy dark mass at the bottom of the illustration is the wall of the carotid artery. The small vessel in the middle shows swollen and reduplicated endothelium, and the surrounding connective tissues are infiltrated with lymphoid and plasma cells.

FREQUENCY OF OCCURRENCE

Syphilitic aortitis is known to be common in paretics. And the lesions here are quite comparable in their type to those of the cranial vessels though modified somewhat by the different anatomic conditions. The presence of perivascular lesions in the cranial vessels in their extracerebral course supports the hypothesis of the invasion of the brain by way of the periarterial lymph spaces, and our *envisagement* of the disease-process as a whole would then be that of a persistent vascular infection with a very even balance between the invasive power of the parasite and the resistance of the host lasting over a number of years, which constitute the incubation period of paresis, with ultimate invasive spread in multiple small foci to the brain parenchyma.

The even balance between attack and defense is an essential in determining the long latent period (from six to twenty years), and is supported by the claim of Fournier and the statistical work of Pilez and Mattauschek that paresis is much more apt to occur in cases of *mild* infection. That the final invasion of the brain takes place in multiple foci is apparent from the clinical course of the disease with its many variations, fugacious paralyses and aphasias and frequent improvement or even complete remissions, and this is well supported by the occurrence of nests or clusters of spirochetes in the brain tissues. There is little difficulty in demonstrating the organism either by the dark-field microscope or in stained specimens if one of these active colonies be encountered, but one may often search over large areas of the brain even in advanced cases without finding such a focus. Marinesco has pointed out that when an apoplectiform attack has accompanied death, thus indicating an exact area for examination, the organism can be demonstrated with great constancy.

Granting the focal character of the lesion it is obvious that the clinical picture will depend on at least two factors: (1) the locus, and (2) the irritative or destructive nature of the invasion. The manic forms of many early cases — hallucinosis and convulsions — suggest the irritative or discharging lesion, while permanent paralyses, aphasias and the progress of dementia are the results of a destructive process.

SUGGESTIONS AS TO METHOD OF TREATMENT

The consideration of paresis as essentially a vascular disease might at first sight be considered as an indication for the intravenous method of arsphenamin therapy as contrasted to the intraspinal and intracerebral, and while the writer still considers this the method of choice it must be remembered that the perivascular spaces are separated from the blood stream by the same very efficient filter — the cerebral

vascular endothelium — as are the brain structures themselves. If, however, we accept the hypothesis that paresis is the terminal stage of a latent or very slowly progressive cerebral arteritis comparable to the cavitation stage in tuberculosis, prophylactic treatment in the form of "follow-up" treatment of syphilitics and intensive treatment of those cases which are occasionally encountered of so-called "laboratory paresis" without psychosis offers much greater promise. This, of course, falls for the most part without the province of the neurologist and psychiatrist and in the hands of the dispensary worker and the general practitioner, but the emphasis on the need of consistent therapy must come from the specialist.