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THE PATHOGENESIS OF TUBERCULOUS MENINGITIS

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Concerning the pathogenesis of tuberculous meningitis, there are two contradictory conceptions. Part of the authors insist on the importance of infection immediately connected with the bloodstream, while others consider the tuberculous foci invading the leptomeninges from the brain, respectively from its adjacent regions, as decisive factors.

1. *Direct infection by way of the bloodstream.* It has been observed long ago that tuberculous meningitis frequently occurs conjointly with miliary tuberculosis. According to *Steinmeier*, tuberculous meningitis occurs in 45 per cent. of miliary tuberculosis cases. According to *Hartwig*'s investigations, this proportion is as high as 2/3. In some instances post-mortem examinations show only a primary complex beside the tuberculous meningitis *(Wallgren* and *Nilson, Kleinschmidt). Huebschmann* declared that tuberculous meningitis is simply a manifestation inherent to miliary tuberculosis. In cases when generalized symptoms are lacking in other parts of the organism, adherents of the hematogenous theory explain the origin of tuberculous meningitis by a minor bacillemia and increased susceptibility of the leptomeninges.

In children, the focus from which bacilli invade the bloodstream is usually the primary complex, endowed with signs of activity *(Gsell* and *Uehlinger, Engel, Wangenheim)*. It is rather exceptional that a primary pulmonary focus in children with tuberculous meningitis should tend toward recovery. The investigations of *H. Koch* report only two cases of calcification or cretaceous transformation of pulmonary foci and lymph nodes, against 255 cases of active tuberculosis. In adults, it is more frequent that bacteria originating from a progressive organic tuberculosis — mostly of the bone, or of urogenital location — break into the bloodstream.

Bacteria may reach the leptomeninges by two different approaches. 1/ by way of the meningeal arteries, 2/ through the chorioid plexus. While the first means of infection is practically identical with hematogenous dispersion of foci found in other parts of the organism *(Skhvortzov)*, contamination through the chorioid plexus is of different character.

The latter was first investigated by *Sepp*. He explained the localization of meningitis by the streaming of CSF. Tuberculosis bacilli starting from the plexus and invading the CSF, would reach from here the cerebral cisterns. Consequently, the heaviest exudates and the major number of tubercles will be located on the base of the brain and on the posterior surface of the spinal cord.

Kment's investigations led to the hypothesis that, as a result of hematogenous dispersion, the chorioid plexus and the tela chorioidea become infected. The course of infection can attain herefrom the leptomeninges through the perivascular lymph spaces, or the CSF may convey the infection to the meninges, respectively the cerebral cisterns. *Engel*, *Futer* and *Prokhorovich*, further *Yerofeyev* are likewise supporting the theory of the plexogenous infection. Animal experiments performed by the latter author demonstrated that the primary important tuberculous alterations noted in cases of hematogenous infection occur in the chorioid plexus.

2. *Direct contamination*. This theory was inaugurated by *Rich* and *McCordock*, though several previous investigations had already suggested that tuberculous meningitis frequently follows the apparition of tubercles in the brain.

In 1887, *Rubens Hirschberg* observed 3 cases of tuberculous meningitis the evolution of which, though widely divergent, comprised dominating cerebral focal symptoms (paralysis, convulsions of epileptic type, aphasia) and in which the symptoms of tuberculous meningitis developed only later. Post-mortem in each case proved the presence of cerebral tubercles, with a fibrous tuberculotic process of productive character at the periphery. *Hirschberg* having collected further 29 similar cases, emphasized in his report the fact that the source of tuberculous meningitis is frequently in these cerebral tubercles.

Trevelyan observed similar cases in 1903. *Bieber* (1911) made careful investigations and found that 13 out of 17 tuberculous meningitis cases revealed a tubercular focus in the brain. Anatomo-pathological and histo-pathological examinations confirmed the connection of the latter with the meningeal process. According to *Bieber*, however, this alteration originates in the leptomeninges, to invade from there the cerebral substance. *Korteweg* stated in 1923 that tuberculous meningitis is, in many cases, a sequel of extrapulmonary tuberculosis. The tubercle bacilli establish themselves on the leptomeninges, where they produce tubercles. These, in turn, are going through phases of growth and colliquation, disseminate the tubercle bacilli into the CSF, and result finally in secondary diffuse tuberculous meningitis.

On basis of numerous investigations *Rich* and *McCordock* in 1929 were the first to prove that direct hematogenous infection is far from playing the outstanding role formerly attributed to it in the pathogenesis of tuberculous

meningitis. Cerebral, or meningeal tubercles invading the subarachnoidal region and infecting the meninges are to be considered the decisive factors.

Rich and *McCordock* analyzed carefully the origin of tuberculous changes. They declared that the intense caseous exudation noted in tuberculous meningitis can be traced as an allergic condition. In order to make these alterations manifest, a very large number of bacilli is necessary. Conditions for the latter possibility are not given during the phase of hematogenous dispersion. Consequently one has to investigate other sources. Careful frontal slicing of the cerebral substance into strips of 2—3 mm showed in 90 per cent. of 82 cases cerebral or meningeal tubercles, closely interrelated with the meninges. Histologic properties proved that the tubercles had been there before the meningitis. *Rich* and *McCordock* considered the tuberculous meningitis as originating from these cerebral or meningeal tubercles. They found this process perfectly identical with the infection of other serous membranes, for instance of the pleura, which becomes infected in the majority of cases through a tuberculous affection of the lungs or lymph nodes breaking into the pleural cavity.

Rich and *McCordock* stated that, in cases of a generalized infection, the evolution of miliary pulmonary tuberculosis and the outbreak of meningitis do not coincide in time — at least not in most cases —, further that the pulmonary change observed and the meningitis show different histological characteristics. Extremely generalized miliary tuberculosis is frequent without correspondent tuberculous meningitis, and vice versa.

The hypothesis of a direct attack is confirmed by data yielded by animal experiments. French authors *(Péron, Armand Delille)* introduced massive doses of tuberculosis bacilli into the carotid artery of the dog. Following the intervention, cerebral microembolisms were noted. Meningitis, however, did not appear, and only few tubercles were seen to develop on the leptomeninges. Tuberculous meningitis was observed upon injecting bacteria directly into the subdural cavity *(Martin, Sicard, Austrian, Manwaring, Soper* and *Dworski, Jousset, Rich* and *McCordock)*.

The investigations of *Rich* and *McCordock* gave the impulse for several control experiments. In the Soviet Union, *Mints* has given the question thorough attention. At necropsy of 73 children deceased with tuberculous meningitis, 39 cases revealed tubercles in the cerebral parenchyma. These displayed the most varied forms of development, from actual necrosis of the cerebral substance to the onset of fibrosis. In some of the cases an active primary complex was present parallel with the cerebral tubercles, while in others miliary tuberculosis appeared. *Mints* consequently stated that in spite of adequate conditions given, cerebral foci alone cannot be considered as the only cause of tuberculous meningitis. According to *Razdolsky, Zhukovsky* and *Ruskich*, cerebral tubercles are nearly always accompanied by tuberculous meningitis. *Aftsin* and *Ivanovskaya* studied 50 similar cases.

They found 5 instances of solitary cerebral tubercles, 3 of meningeal ones, while 11 cases presented more or less manifest conglomerate tubercles on the meninges. *Futer* investigated 180 cases of tuberculous meningitis treated with streptomycin. He noted that only 10 per cent. showed a localization of the process on the meninges, in the remaining cases a more or less distinct tuberculous alteration of the cerebral substance was registered. Some cases were observed in which internal organs were not affected by tuberculosis, though highly advanced meningitis was present.

Ageytchenko emphasized the specific interrelation of tuberculous meningitis and age. His observations resulted in the recognition that though it is known that invasion by cerebral foci provokes consequential meningitis in adult life, this way of infection is negligible in infants.

Western literature is equally rich in control investigations. The data given by *Rich* and *McCordock* have been confirmed by *McGregor* and *Green*; *McGregor*, *Kirkpatrick* and *Craig*; *McMurray*, *Beitzke*, *J. Schwarz*, *Auerbach*, further by *Radman*, while the experimental results of *Beres* and *Meltzer*, *Achelis*, *Raggins* contradict the above-mentioned observations.

While in the past this discussion appeared merely theoretical, the elucidation of pathogenesis has attained an essentially practical importance since the application of streptomycin therapy. The fact whether tuberculous meningitis has been engendered by invasion of cerebral foci, or by hematogenous infection, exerts a major influence both upon the methods of treatment and the prognosis of the disease. This is why we consider the study of the pathogenesis of tuberculous meningitis imperative, availing ourselves of the large material provided by our Institute.

Own investigations

From January 1946 onward the 1st Department of Pathological-Anatomy and Exp. Cancer Research offered us post-mortem material comprising 339 cases, deceased as a result of tuberculous meningitis or miliary tuberculosis. The majority of this material comprised infants and children. These patients had been subjected to longer or shorter streptomycin therapy at the 1st and 2nd Departments of Paediatrics or at the State Infant Sanatorium (Szabadság-hegy, Budapest). We are indebted for the clinical data used in the present report to Professors P. Gegesi Kiss and G. Petényi, and Director I. Flesch. Adult cases were only rarely observed.

Among the 339 cases quoted, basilar meningitis and miliary tuberculosis were found together in 196 instances, tuberculous meningitis without concomitant miliary tuberculosis in 118 instances, miliary tuberculosis in the absence of tuberculous meningitis in 25 cases. These data consequently prove

that, though tuberculous meningitis and miliary tuberculosis were noted conjointly in 57·8 per cent. of our material, 34·8 per cent. manifested solely meningitis, and 7·4 per cent. miliary tuberculosis alone. (See Table I.) Even

TABLE I.

	Number of cases	per cent
Total number of tuberculous meningitis and miliary tbc cases autopsied since 1. January 1946.....	339	
Meningitis + miliary tbc.....	196	57,8
Meningitis alone	118	34,8
Miliary tbc alone	25	7,4

generalized miliary tuberculosis in its most extreme form was noted without involvement of the leptomeninges, while diffuse exudative tuberculous meningitis, with considerable exudation and numerous tubercles, occurred without generalized miliary tuberculosis, manifesting only small, distinctly circumscribed primary complexes.

These data suggest above all that tuberculous meningitis cannot be considered as a mere component of generalized miliary tuberculosis and that it may develop in the absence of miliary tuberculosis.

We have studied 200 cases of tuberculous meningitis in view of establishing the percentual occurrence of tubercles in the cerebral substance or in the meninges, investigating whether the size and histopathologic aspect of the tubercles would prove their priority to the onset of meningitis, and whether their localization could be made to account for the meningitis. Our studies included 102 male and 98 female subjects, the youngest 3 weeks, and the oldest 40 years of age.

Methods

After removing the brain, we described the changes present on the meninges. Thereafter, fixing the brain at least a month in a 4% formalin solution, we proceeded to cut frontal sections of 3—5 mm, keeping all the while attention to tuberculous alterations present in the cerebral parenchyma. Suspicious foci were subjected to transillumination to become clearly outlined, owing to their diverging structure. Foci, which appeared macroscopically as tubercles were investigated histopathologically.

To complete our investigations we examined the spine, the dura, and the spinal cord. Results gained in this manner were finally brought to fit into the row of observations regarding tuberculous alterations noted within the entire organism.

Results

200 cases of tuberculous meningitis investigated showed 147 cases displaying a tuberculous focus in the central nervous system or in its vicinity (73·5%). 142 of these satisfied the requirements outlined above and could consequently be

regarded as immediate cause and origin of meningitis (71%). In 5 cases, the focus either failed to show immediate contact with the meninges, or it was histologically proven to have originated at a later date than the foci which could be assumed to be the cause of meningitis. 93 were cerebral, (46·5% of the total), 43 were meningeal tubercles (21·5%). We discovered in addition 2 tubercles in the dura, 1 in the cauda equina, while in 3 cases tuberculous spondylitis breaking into the spinal canal was doubtlessly found to have been the cause of meningitis. This gives a total of 3 per cent. 58 cases yielded no foci, either in the brain or in the surrounding region. These cases amount to 29 per cent. (see Table II).

TABLE II.

200 cases examined in detail showed	Number of cases	per cent
Circumscribed tuberculous alteration in the central nervous system or in its vicinity	147	73,5
As focus could be regarded	142	71,0
Cerebral tubercle	93	46,5
Meningeal tubercle	43	21,5
Tubercle of the dura	2	3,0
Tubercle of the cauda	1	
Tuberculotic spondylitis	3	
No focus present	58	29,0

The occurrence of foci and their respective frequency in the diverse regions is to be found in Table III.

TABLE III.
Localization of foci within the central nervous system

Order	Occurrence	Number of cases
1	Frontal cortex	65
2	Temporal cortex	53
3—4	Occipital cortex	47
3—4	White substance of hemispheres	47
5	Parietal cortex	38
6	Cerebellum	33
7	Pons	24
8	Insula	19
9	Basal ganglia	13
10	Peduncle	12

Discussing each kind of these tuberculous foci, we begin by analyzing cerebral tubercles.

They are located mostly in the hemispheres of the cerebrum, at the borderline of the cortex and the white substance, or cortical substance. They most frequently occur in the fronto-temporal, then in the occipito-parietal lobes. Another site of occurrence comprises the white substance of the hemispheres, the pons, insula, less frequently the basal ganglia, peduncle, spinal cord, hypothalamus and bulb. (Fig. 1.)

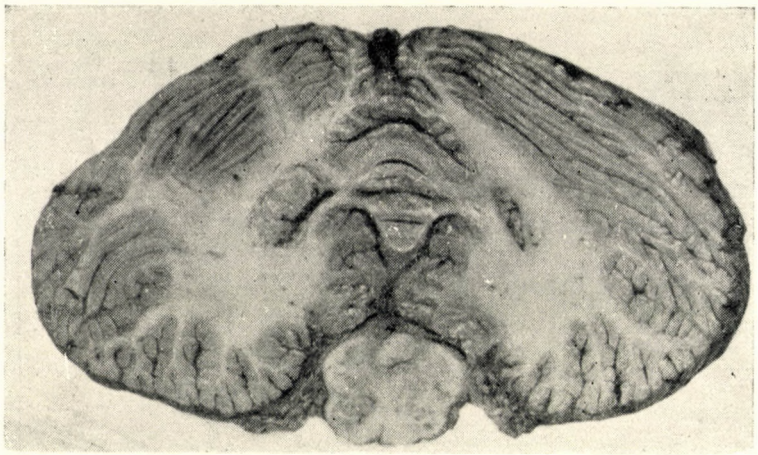

Fig. 1.
Pea-sized, caseous focus in the medulla oblongata, immediately below the obex.

The number of cerebral tubercles is equally highest in the cortical substance of the cerebrum. Most tubercles were observed in the frontal lobes, then in the occipital and parietal lobes, finally in the white substance of the hemispheres, temporal cortex and cerebellum. We observed further numerous tubercles in the insula, pons and peduncle. (See Table IV.)

Cerebral tubercles are mostly multiple (Fig. 2), rarely single nodules. (Fig. 3). They are of widely differing size. Beginning with the elementary tubercle, for the detection of which a microscope is needed, up to the tuberculoma, large as a green nut, all sizes are met with. Anyhow, the millet-, or small pea size is the most frequent one. It may be stated in general that the more numerous the tubercles the smaller their size, whereas solitary tubercles are reaching the maximal size. Tubercles are round, sometimes scalloped at the edge. Their specific greyish-brown tinge makes distinction easy from the surrounding cerebral substance. Their cross-section is homogeneous, of a dry consistency, the centre of larger foci is soft. (Fig. 4.) Around the larger foci a capsule of connective tissue may develop. This

TABLE IV.

Order	Occurrence	Number of foci
1	Frontal cortex	375
2	Occipital cortex	302
3	Parietal cortex	202
4	White substance of hemispheres	198
5	Temporal cortex	128
6	Cerebellum	111
7	Insula	64
8	Pons	60
9	Peduncle	42
10	Spinal cord	21

tissue stands out sharply against the surrounding cerebral substance. In sporadic cases the tubercles become calcified. (Fig. 5.)

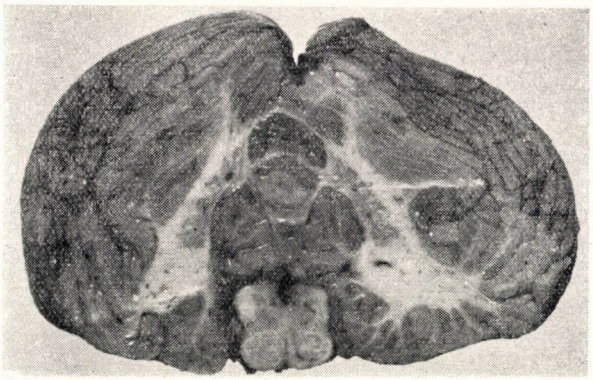

Fig. 2.

Lentil- and pea-sized, well circumscribed foci on the left side, located in the biventer lobe, on the border of the quadrangular and superior semilunar lobe, within the superior semilunar lobe, under the pia and in the vermis.

Smaller cerebral tubercles can seldom be found without performing serial sections or transparency. In other cases, the intense local process developing around the tubercles results in their discovery. Namely it occurs frequently that a tubercle situated in the cerebral substance grows and forms the centre of a developing exudative, caseous meningitis, or meningoencephalitis. When this happens, the dense, productive foci within the exudate become clearly outlined. In other cases, the meninges above cerebral foci manifest a fibrous thickening, they are milky white, and eventually adhere to the dura. The area affected by the fibrous meningeal process is often surrounded by an area of tubercles

of the size of a penny, in other cases there is a handbreadth' area of disseminated millet-sized tubercles. These alterations are particularly suggestive when they develop on the convexity, on a region usually not, or only slightly affected

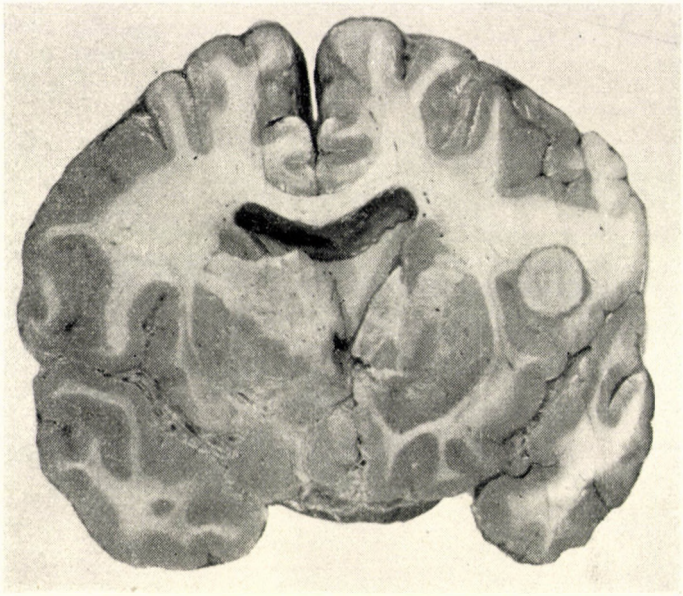

Fig. 3.
Hazelnut-sized solitary tubercle above the right insula.

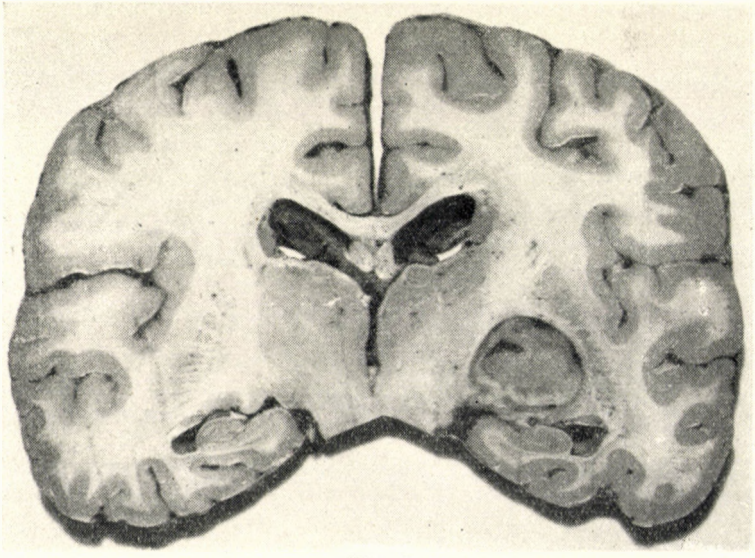

Fig. 4.
Softened tubercle, of pigeons-egg-size, in the right lentiform nucleus.

while the leptomeningeal regions at the opposite side are smooth.

Around the focus breaking into the cerebral ventricle, the ependyma is dotted with numerous tubercles, the chorioid plexus, transformed into a fibrous fascicle, adheres to the ventricular wall and is covered with a fibrinous-gelatinous exudate.

The histologic aspect of cerebral tubercles varies. Initial changes are mainly noticeable upon tubercles located close to the meninges, or the

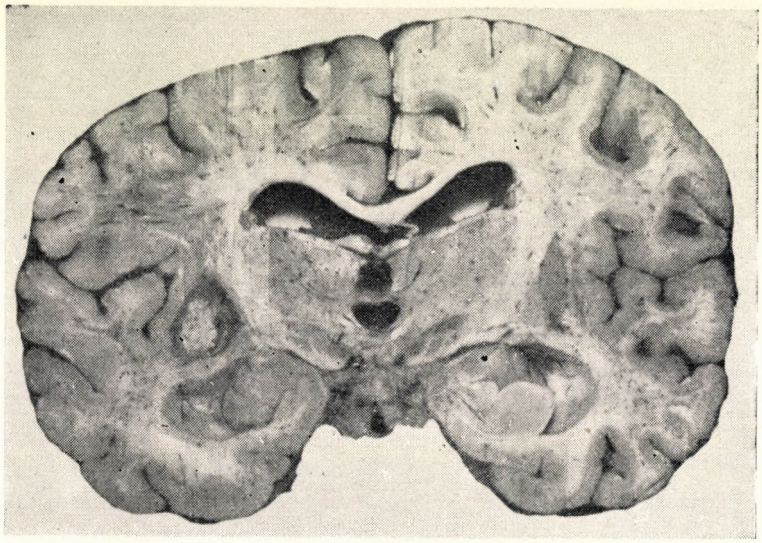

Fig. 5.
Calcified hazelnut-sized cerebral tubercle, seated in the right putamen, claustrum and insula.

cerebral ventricles of recent or non-treated cases. In this area, the ganglionic cells within the millet-sized foci become bloated and dissolved. Some leucocytes are to be observed in the centre, with a proliferation of glial cells on the periphery. This alteration, with its light coloration and foamy structure is well outlined against the neighbouring cerebral substance. By means of Ziehl—Neelsen staining, numerous tubercle bacilli are found in the tubercles.

Relatively immature foci are chiefly composed of leucocytes with shrunken pyknotic nuclei and destroyed cells forming a mass of débris within the centre. Around the foci, there is a distinct infiltration of round cells. The glia is condensed, the walls of the surrounding small arteries and arterioles stain homogeneously, without revealing any structure. The lumen is crowded with erythrocytes, the adventitia manifesting round cell infiltration. Broken, destroyed vessels cause in some cases hemorrhage. Ganglionic cells, with swollen ballooned nuclei, and phagocytes containing lipoids, can be observed.

Later on, caseation takes place in the centre of such foci (see Fig. 6). Their border is composed of leucocytes bearing pyknotic nuclei, nuclear shadows and débris. There are numerous Koch's bacilli in these foci. On the periphery of the necrotic zone, round cell infiltration is intensified, epitheloid cells appear, followed later on by giant cells of the Langhans type.

These productive foci are developing particularly if evolution lasts long under the effect of streptomycin. They also appear in acute cases

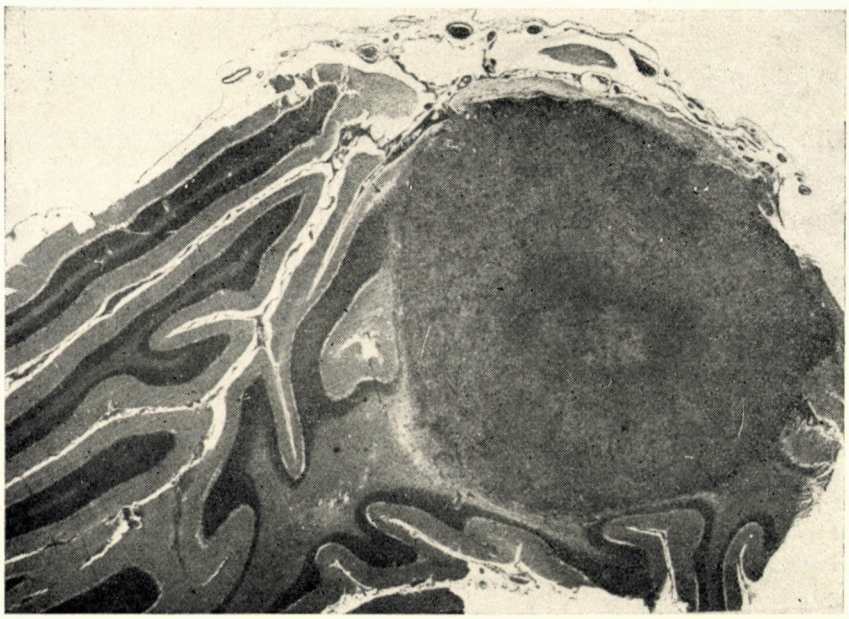

Fig. 6.
Cerebellar tubercle, with a caseous centre.

but in such instances tubercles are situated further away from the meninges. Foci of such long standing consist of epitheloid and giant cells, their centre is hyalinous or caseous, and in the latter case they contain a granulous precipitate of calcium salts. Consequently, haematoxylin staining of these tubercles results in a much darker colour than that of the environment.

We have encountered hazelnut-sized, entirely calcified cerebral tubercles with traces of ossification leading to tuberculous meningitis. Around the calcified tubercles, the development of considerable gliosis and fibrous connective tissue could be observed in the cerebral substance. Glial tissue may substitute smaller tubercles, forming there specific round or star-shaped foci.

Though these old productive foci point to a healing of the process, they still contain numerous Koch bacilli and the possibility of a flare-up is by no means negligible. This becomes naturally even less probable, if a fibrous

capsule has been formed around the tubercle. The chances of propagation are certainly much more favourable in the foci presenting rapid caseation. In these cases the morbid process may often be observed during the act of invading the depth of a sulcus or its surface, producing a gelatinous, fibrinous exudate between the meninges. The process may equally spread into the ventricles and it is sometimes possible to observe the caseous mass pouring into ventricular cavities (Fig. 7.). Histological findings demonstrate that foci which macroscopically seem to lie far from the meninges or ventricles can still bring about meningitis. The extension of the process from the tubercles towards the lepto-

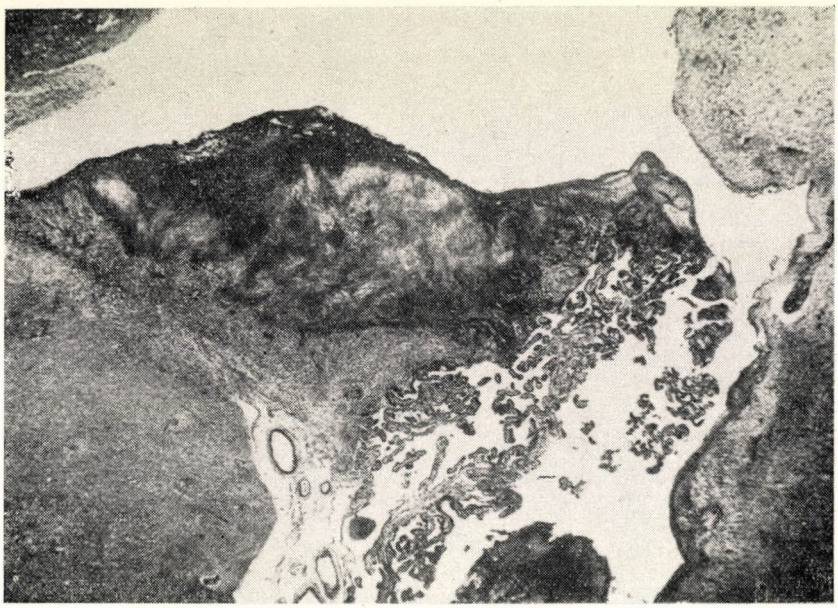

Fig. 7.
Several caseous foci within the IIIrd ventricle have invaded the chorioid plexus, which is covered by fibrinous exudate and adheres to the ventricular wall.

meninges or into the ventricular system through the perivascular lymph-spaces is frequently noted. The Virchow-Robin spaces are dilated, a perivascular caseous exudate may occur. In other cases considerable perivascular round cell infiltration is present (Fig. 8.), further tubercles of microscopic size built up of epitheloid and even giant cells may appear in a localisation corresponding to the perivascular spaces.

Another group of foci is composed of meningeal tubercles. These are usually numerous, with the aspect and size of a flattened pea or black pepper. They stand out as dry nodules from the cerebral substance (Fig. 9.) and are frequently localized in the depth of a sulcus, protruding from the surface like mushrooms. In other instances, they dilate the sulcus, staying hidden within

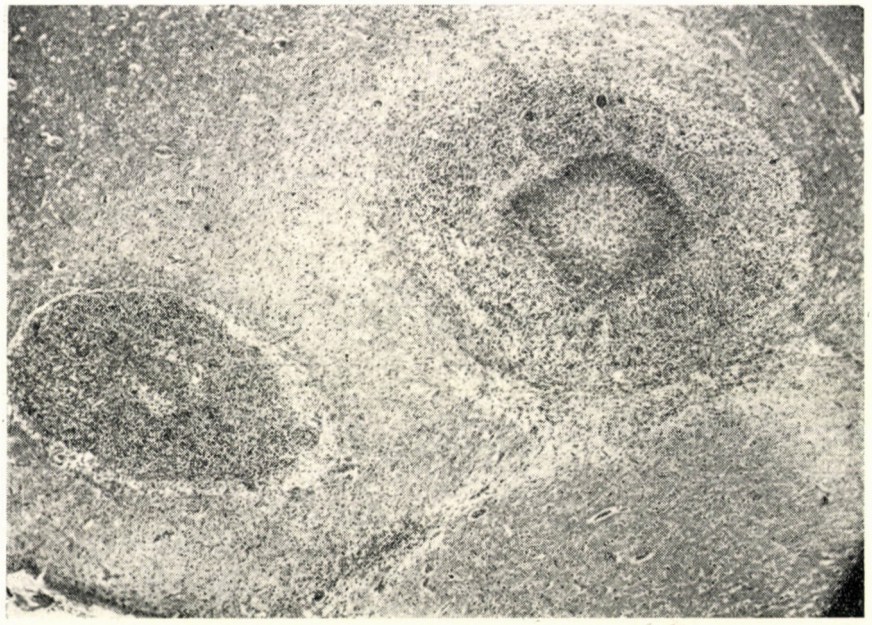

Fig. 8.
Expansion of the tuberculotic process, starting from the cerebral tubercle and reaching the meninges through the perivascular spaces.

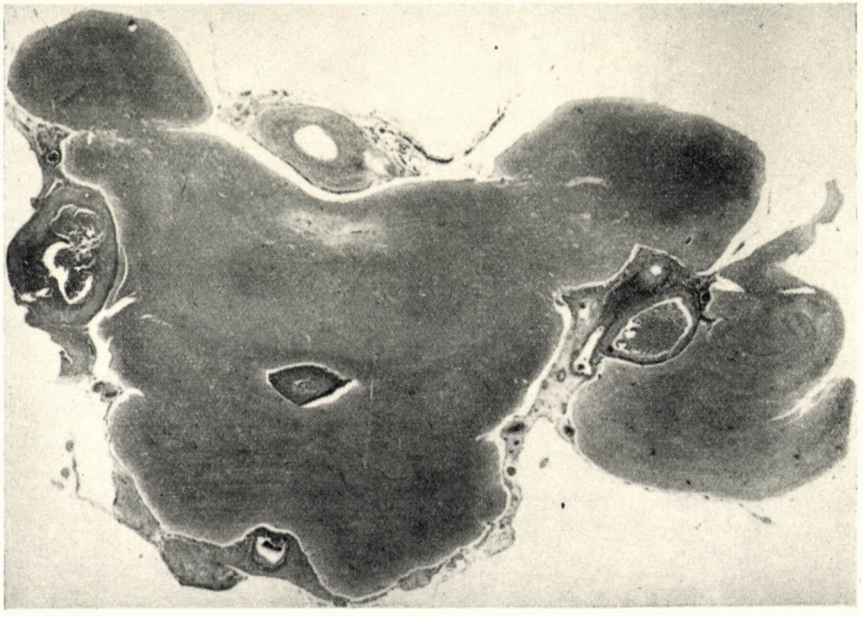

Fig. 9.
Multiple softened meningeal tubercles, seated bilaterally in an area between the fissura hippocampi and the base of the pons.

its depth and appearing only on cross sections. It occurs that several meningeal tubercles localised within a deep sulcus, get coalesced during growth and form a conglomerate tubercle. The centre of these tubercles is caseous, surrounded by epitheloid cells, fibroblasts and granulation tissue containing giant cells of the Langhans-type.

Meningeal foci are seldom seen to form those flatly prominent, fibrous tubercles taking the size of a penny or of the handbreadth of an infant, which are designated as »tubercles en plaques«.

We noted 2 instances of these tubercles. The first was located on the convexity of the right frontal lobe and was composed of coalescing bean- and child-palm sized foci. (Fig. 10.) In relation to the alterations, the lepto-

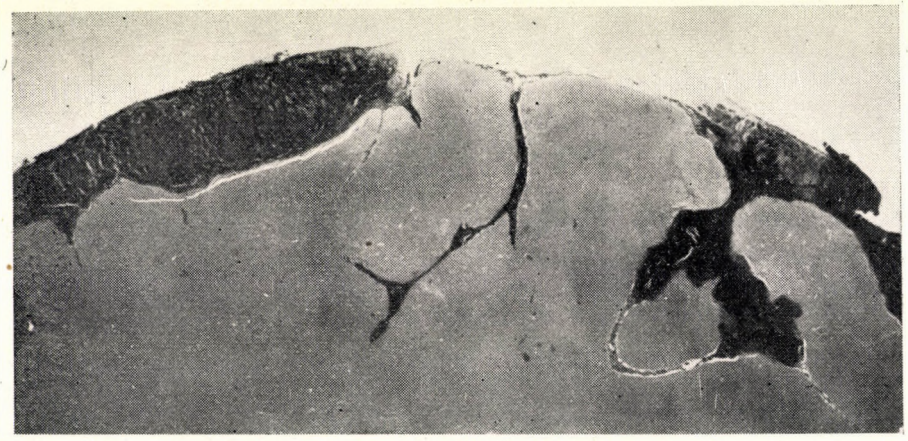

Fig. 10.

Tubercle en plaque, correspondent to the frontal convexity. The granulomatous, highly fibrous tissue penetrates into the depth of the sulci, but does not invade the cerebral substance.

meninges adhered firmly to the dura, so that the removal of the brain had to be effected by separation from the dura by a knife. The process passed deeply into the sulcus, but did not penetrate into the cerebral substance and only destroyed it by the compression exerted. Histologic findings proved that it consisted of fibrous conjunctive tissue, with disseminated caseous areas, and at the periphery of granulomatous tissue, composed of epitheloid cells and fibroblasts.

The second tubercle en plaque was located in relation to the pons, it was of penny size, and the pons adhered to the clivus in the affected area. Gelatinous exudation occupied the periphery. The histologic picture showed epitheloid and giant cells composing a granulomatous tissue manifesting signs of hyalinous transformation.

Two cases of meningitis could be traced to tuberculosis of the dura. The first presented 5 caseous nodules of pea or shelled hazelnut size, localized on the internal surface of the dura, in the area of the hemisphere's convexity, right

and left of the superior sagittal sinus (Fig. 11.) In the region corresponding to the foci, the dura adhered to the arachnoidea, which was of a granular appearance and contained numerous millet-sized tubercles. The majority of nodules was caseous, and contained epitheloid and Langhans' giant cells with a large number of Koch bacilli. On their periphery, a fibrous capsule could be demonstrated. In the second case, a multitude of lentil-sized tubercles, displaying an identical structure, situated on the internal surface of the dura near to the cervical segment of the spinal cord, could be considered as the cause of the diffuse tuberculous meningitis.

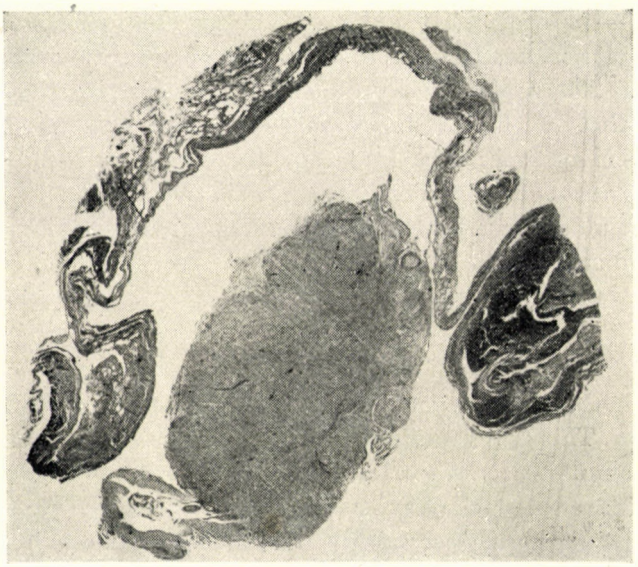

Fig. 11.

Bean-sized, caseous tubercle, situated on the lining of the dura, and recognized as the source of diffuse tuberculous meningitis.

We have noted one case where the source of meningitis was a conglomerate of bean-sized tubercles seated between the roots of the cauda equina. A definite productive reaction distinguished the peripheral area. The spinal process unequivocally dominated the entire aspect of the meningitis. Histological examination showed that it was composed of epitheloid and giant-cell tubercles, with a caseous centre containing demonstrable tuberculosis bacilli.

In 3 cases, the tuberculous meningitis originated from tuberculous spondylitis. The patients, subjected to protracted streptomycin therapy on account of spondylitis, had developed meningitis during the treatment. Autopsy revealed that the tuberculous caries had broken into the spinal canal; the meningeal process was most accentuated in its vicinity.

Origin and evolution of tuberculous foci

Studying the alterations encountered occurring conjointly with tuberculous lesions in other parts of the organism, we found that tuberculous foci of the brain and its surroundings are the result of hematogenous infection. The origin of the tuberculous process is generally a primary complex. This view is confirmed by the fact that cerebral tubercles often develop at a time, when the primary complex is the only tuberculous process within the organism.

From the 339 cases subjected to investigation, 306 disclosed primary foci or caseous tuberculous hilar, paratracheal and mesenterial lymphnodes. Among these there were 17 cases of calcification, 7 of pronounced scarification. In 17 instances — mainly in adult subjects — the site of invasion was a progressive organic tuberculosis mostly of the joints and bones. 16 cases out of 339, and 10 out of 200 systematically studied ones failed to show tuberculous changes in other parts of the organism. Each of the 10 was found to manifest tuberculous foci in the brain, or around the central nervous system, and these were without exception large productive foci, at least of the size of a pea surrounded by a fibrous capsule. This proves that dissemination had taken place some time before, the cerebral foci remaining latent while the primary complex healed and was no longer traceable at post-mortem examination.

An argument in favour of the hematogenous origin is the parallelism of the number of foci in the nervous system with the degree of generalization observable in the organism. This was especially true in widespread miliary tuberculosis, when numerous millet-sized tubercles, possibly over a hundred, developed in the cerebral substance and led to miliary cerebral tuberculosis (see Fig. 12). In such cases it could be established by careful investigation that some tubercles had grown larger than the rest, and eventually fused with neighbouring tubercles, forming in this fashion cloverleaf-shaped foci in the depth of some sulcus. Subacute miliary tuberculosis produced larger cerebral foci.

The major part of tubercles, as stated before, originated chiefly from bacillemia, arising from the primary complex. Generalization takes place when allergy and resistance of the organism have not yet developed. This is confirmed by the histologic character of the foci, inasmuch as (in the beginning the evolution of specific granulation tissue is missing and the lesions are more of the exudative type. These foci increase rapidly in size and bring about diffuse exudative tuberculous meningitis whenever they are located near the meninges or the ventricles. If, however, they are seated deeply in the cerebral parenchyma, there is a good chance of encapsulation, assisted by the favourable conditions produced by the developing resistance of the organism. This is how the hazelnut or nut-sized tubercles leading to clinical symptoms are developed.

The rest of cerebral foci develops as the result of late dissemination. The latter will take place whenever and wherever a progressive tuberculous focus is present in the organism. Considering, however, that by that time the resistance of the organism has been fully developed, the growth of foci is slower and there is a possibility of encapsulation.

It is possible, however, to demonstrate tuberculosis bacilli in such incapsulated foci, which are a constant menace to the organism. The decrease of resistance of an

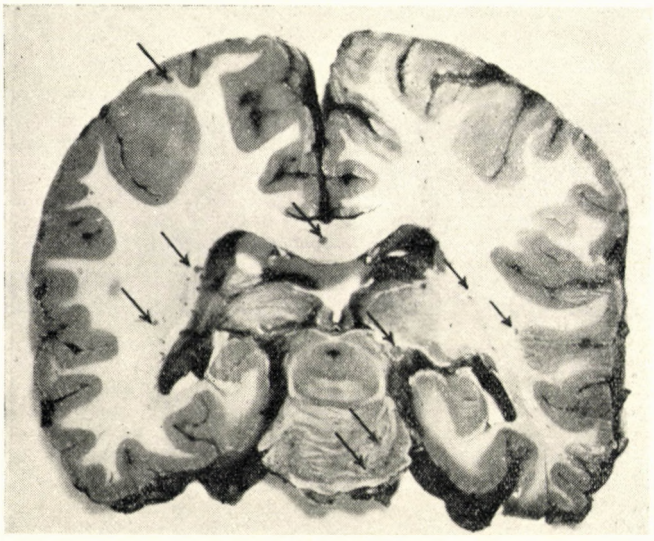

Fig. 12.

Miliary cerebral tuberculosis : several tubercles of pinhead size can be observed on the border of the cortex and white substance, in the pons, — further, a well circumscribed tubercle can be noted inside the corpus callosum.

organism is subject to outward and inward influences. These will render infectious agents in the foci more virulent. A focus which had been encapsulated may disintegrate and the discharged bacilli may bring about a diffuse tuberculous meningitis. This pathogenesis is well illustrated by the following case.

A male subject 40 years of age had suffered during adolescence from a specific pulmonary affection which had healed after 6 months and did cause no inconvenience in later years. 8 years before admission, symptoms of hypertension and increased intracranial pressure had been recorded. After unsuccessful conservative treatment, lumbodorsal splanchnectomy according to Smithwick was performed, following which the patient developed headaches. After the second intervention, the patient's condition became worse, and amblyopia, followed by loss of consciousness and death ensued 3 weeks after the second

intervention. Autopsy revealed tubercles en plaques localized on the convexity beside tuberculous meningitis. It is evident that a decrease of resistance induced by the operation had activated local meningeal processes of long standing and of fibrous-hyalinous character bringing thus about a diffuse tuberculous meningitis of lethal outcome .

Tuberculous meningitis being a disease common in infancy and childhood, cerebral tubercles are also more common in early years. If tuberculous meningitis happens to develop in the adult, cerebral tubercles may also occur. The correlation between age and foci is demonstrated in Table V.

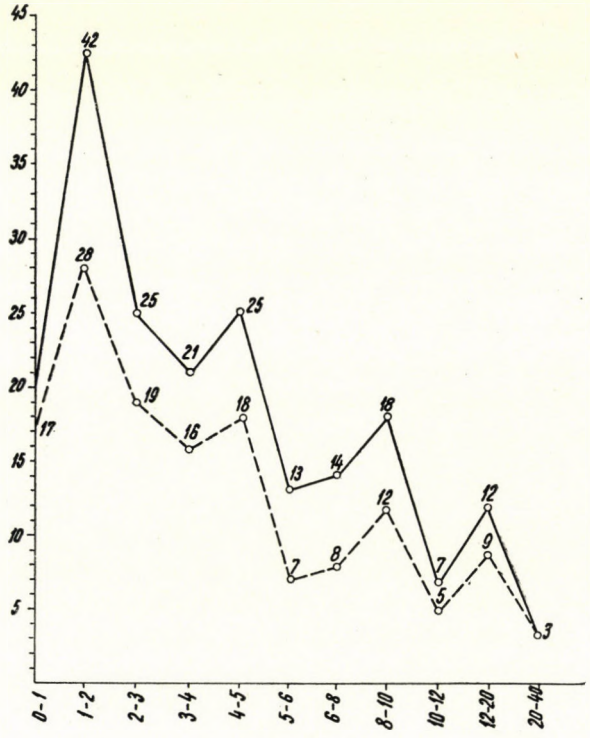

TABLE V.

Distribution of subjects according to their age. Interrelation of tuberculous foci in the brain and age. On the abscissa, age of patients ; on the ordinate, number of cases. The upper curve indicates the total number of cases, the lower one only those in which a cerebral focus was found, which could be considered as source of tuberculous meningitis.

Results

In 71 per cent. of the 200 cases discussed were there present in the central nervous system or in its neighbourhood foci from which tuberculous meningitis may have started. There are among the cases two definite groups in

which foci in the nervous system occurred in a much higher percentage. The first group included cases of tuberculous meningitis in which no other tuberculous change occurred in the organism. The second group was composed of cases with relapsing tuberculous meningitis.

There were 10 cases in which no tuberculous change apart from meningitis was present. Each case yielded a focus in the cerebral substance, or upon the meninges, which fully accounted for the origin of tuberculous meningitis.

Among the 200 cases of tuberculous meningitis there were 16 relapsing ones. Relapsing tuberculous meningitis has been known since the institution of streptomycin therapy. The specific changes on the leptomeninges may disappear as a result of streptomycin therapy, symptoms as well as alterations of the CSF may regress. Remission may last for a long time; we have observed cases when the child remained in what seemed good health for 2 years. In other instances only a few months of relief were gained. After a while, however, the symptoms of tuberculous meningitis returned, and became fatal in spite of the streptomycin and adjuvant therapy introduced.

15 of the 16 relapsing cases of tuberculous meningitis observed by us had a focus within the central nervous system or in neighbouring regions. Part of the cases manifested foci composed of pea- or bean-sized meningeal tubercles provided with a wide, fibrous capsule (Fig. 13). Their inside consisted of a caseous mass in which tbc bacilli were demonstrable. In other instances foci similar to meningeal tubercles were noticeable in the cerebral parenchyma. In a single case of relapsing tuberculous meningitis, in which a focus could not be demonstrated, generalized miliary tuberculosis was present and the hypothesis that the bacilli reached the meninges by way of the bloodstream seemed justified.

The question remains, in which way tuberculous meningitis had been brought about in cases in which the central nervous system and its immediate vicinity disclosed no focus upon investigation. Negative results may be partly explained by inexact technique, — small tuberculous foci may namely remain undetected in the cerebral substance. Besides, it must be assumed that part of the tuberculous meningitis cases are the result of hematogenous dissemination. Even so, it is striking that though part of the cases is accompanied by generalized miliary tuberculosis of the organism, other cases fail to manifest generalized phenomena and the primary complex is associated solely with tuberculous meningitis.

It doubtlessly follows from the above data that even in cases of tuberculous meningitis in which the absence of foci would point to a hematogenous pathogenesis, bacillemia alone cannot be made responsible for the process. The factor allied to bacillemia in allowing the process has not been cleared and as to its nature one is left to conjectures.

In this sense, the vessel-factor, investigated by *Ageytchenko*, probably plays some role. The part of cerebral and meningeal vessels in the evolution of tuberculous meningitis has been studied by several Soviet authors.

The investigations of *Margulis*, *Skhvortzov*, *Strukov* and *Abrikosov* have proved the fact that infection invades the central nervous system when the vascular barrier is being damaged, when hyperergic alterations occur in the vessels. The nature of immuno-biological changes leading to hyperergic vessel alterations and barrier damage is still a question waiting for answer.

The chorioid plexus is likewise a factor of importance, to which a considerable role in tuberculous meningitis has been attributed in the investigations of *Sepp*, *Yerofeyev* and *Kment*.

Fig. 13.

Pea-sized tubercle in a fibrous capsule, below the infundibulum, from where relapse of an apparently recovered tuberculous meningitis started. On both sides, masses of gelatinous, partly caseous, exudate.

Alterations of the vascular factor and of the chorioid plexus are among the problems our Institute has been also studying. Our own observations will be published elsewhere. The investigations hitherto performed conclude in the fact that certain vascular alterations, which cannot be discussed here in detail, or tubercles found in the chorioid plexus, may ,in certain cases, play an important role in the development of tuberculous meningitis.

Practical conclusions

The above investigations have led us to conclude that in the majority of cases the development of tuberculous meningitis is being initiated by

cerebral or meningeal tubercles. The latter reach in the course of their growth the meninges or, less commonly, break into a cerebral ventricle. This type of pathogenesis was particularly frequent in relapsing tuberculous meningitis and in cases in which other parts of the organism were exempt of tuberculotic process.

Acquaintance with cerebral or meningeal focal lesions makes it possible to understand those cases in which the presence of Koch bacilli in the CSF is not associated with meningeal symptoms. These bacillar findings do not entail an actual tuberculous meningitis, they are, however, a likely proof that a tuberculous focus is developing within the central nervous system, with the corresponding menace of tuberculous meningitis (serous meningitis of Lincoln). The immediate administration of intraspinal streptomycin is consequently indicated whenever such findings are disclosed.

When tuberculous foci have actually developed, and meningitis has become manifest, the chances of recovery are much poorer, though we have observed smaller tubercles being replaced by glial tissue under the effect of streptomycin. These cases are, however, rare exceptions. According to several authors *(Chiari, Debré, Thiefry* and *Brissaud, Ruzicska, Zollinger)*, cerebral tubercles have a poor prognosis. Larger tuberculous foci in the brain may even soften under the influence of streptomycin therapy *(Péró)*.

The feeble tendency toward recovery in cerebral tubercles is explained by several factors. *Baggenstoss, Feldmann* and *Hinshaw*, effecting streptomycin concentration-tests in the cerebral substance, have demonstrated that the latter was free of streptomycin though the CSF showed a high concentration of the drug.

According to *Béguin*, streptomycin is unable to reach a high concentration in the caseous mass, so that the pathogenic agent is at liberty to multiply within the tuberculous focus. This process is furthered by the acid reaction developing in the caseous foci, which, according to *Abraham* and *Duthie* neutralizes the antibacterial effect of the alkaline streptomycin.

These demarcations, limiting the curative possibilities of tuberculous meningitis, are increasingly valid for relapsing tuberculous meningitis. The fact that we were able to discover tubercles of old standing in the brain or upon the meninges in 93 per cent., presented the clue to an eventual relapse. The poor prognosis of relapsing cases may be explained by the phenomenon that tuberculosis bacilli liberated from the focus invade the meninges when resistance to streptomycin has developed after the first treatment *(Madigan, Swift, Brownlee* and *Wright)*.

In view of the fact that these tuberculous foci may lead at any time to a flaring up of the meningeal process, it is imperative that exact neurological investigations should be made for the detection of tubercles in cases of tuberculous meningitis registered as »recovered«. In part of the cases there is a fair chance of success since — according to our observations — the tubercles found in relapsing

meningitis are of fair size and frequently occur in groups. As a rare exception, we may mention cases in which calcified foci were detected by X-ray examination.

Summary

Investigation of 200 cases of tuberculous meningitis led to the conclusion that in the origin of the process, tuberculous foci within the central nervous system or its immediate vicinity are playing the decisive role. They invade the meninges either by direct contact or through the perivascular lymph spaces (71%). In 93 cases foci were located in the cerebral or spinal substance (46·5%), 43 cases yielded meningeal tubercles (21,5%), 2 cases tubercles on the dura, 1 in the cauda equina. Finally, in 3 cases the source of meningitis was tuberculous spondylitis breaking into the spinal canal (3%). In 58 cases (29%) we failed to demonstrate focal findings, but even these cases of meningitis can hardly be ascribed to hematogenous dissemination alone, and other factors (vascular factor, chorioid plexus tuberculosis) must also be taken into account.

Attention must be called to cases devoid of any other tuberculous change in the organism. Out of 10 such cases of tuberculous meningitis each presented a tubercle in the central nervous system or its nearby regions. We examined 16 cases of relapsing tuberculous meningitis, in 15 of them (93,6%) the original focus was found in the brain.

Relapsing tuberculous meningitis is induced by the breaking out and into the meninges of tubercles, encapsulated after the first attack once more. The prognosis of such cases is usually a poor one.

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ПАТОГЕНЕЗ ТУБЕРКУЛЕЗНОГО МЕНИНГИТА

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Резюме

В 200 случаях туберкулозного менингита наблюдения авторов указывают на то, что при возникновении процесса решающую роль играют образующиеся в центральной нервной системе, или по ее близости, туберкулезные очаги, которые или непосредственным расширением, или же через периваскулярные лимфатические щели инфицируют мозговые оболочки (71%). Из всех очагов 93 размещались в веществах мозга (46,5%). 43 представляли собой бугорки в оболочках головного мозга (21,5%), в двух случаях авторы наблюдали очаги в твердой мозговой оболочке, в одном случае в конском хвосте, а в трех случаях источником менингита был проникнувший в позвоночный канал туберкулезный спондилит (3%).

В 58 случаях (29%) авторы не могли доказать присутствие такого очага, однако в большинстве этих случаев возникновение туберкулезного менингита нельзя объяснить только гематогенной диссеминацией и необходимо принимать во внимание и другие факторы (фактор крови, туберкулез сосудистого сплетения).

Авторы особенно подчеркнуп те случаи, при которых они в других местах организма не нашли изменений, указывающих на туберкулез. В 10 случаях такого туберкулезного менингита они в каждой из этих случаев могли найти бугорки в центральной нервной системе или по ее соседству.

Авторами были исследованы 16 случаев возвратного туберкулезного менингита. Среди этих они в 15 случаях (93,6%) нашли исходный очаг в мозгу.

Следовательно рецидирующий туберкулезный менингит возникает таким образом, что инкапсулированные при первом процессе бугорки опять воздействуют на оболочки. В таком случае прогноз в общем неблагоприятнее.