SARCOIDOSIS OF THE CENTRAL NERVOUS SYSTEM*

C. L. ASZKANAZY, B.A., M.D.

[toronto, canada]

Since Boeck (1), in 1899, first described the skin lesions of sarcoidosis and Schaumann (2), in 1914, the systemic form of the disease, sarcoidosis has aroused much interest among clinicians and pathologists alike. The etiology is still obscure. The theory that it is an atypical form of tuberculosis has many defenders, although it has never been proved bacteriologically. That it occurs in a benign form much more commonly than clinically suspected, is shown by the frequency with which it is found in lymph nodes removed because of carcinoma of the breast. After Winkler (3) had first described sarcoid lesions in the peripheral nerves, Heerfordt (4) reported cases of uveo-parotid fever with cranial nerve involvement. According to Levin (5), half of the patients with uveo-parotid fever suffer from cranial nerve palsies. Since then an increasing number of cases of sarcoidosis with neurological symptoms have been reported. Colover (6), in 1948, was able to collect 115 cases from the literature and added 3 of his own. Although the peripheral nerves are usually involved, resulting in peripheral neuritis or cranial nerve palsies, the brain and pituitary gland are not infrequently the seat of the disease. In a series of 22 fatal cases, Ricker and Clark (7) found 3 with involvement of the central nervous system. Because of the usually benign course of the disease, few cases are on record in which it was possible to examine histologically the lesions in the central nervous system. Among 20 cases of sarcoidosis, proved by autopsy in the Department of Pathology at the University of Toronto, 3 showed lesions in the central nervous system. These, with the addition of 2 others, from which the material was obtained at operation, are reported in this paper.

Case Reports

Case 1. History: A previously healthy woman (M. S., NP: 2/40) gradually developed, at the age of 52 years, symptoms of a cord lesion at the level of the first thoracic segment. One year after the onset of symptoms, an extensive laminectomy of the cervical and thoracic regions was carried out. The only abnormal finding was that the spinal cord appeared small, and a diagnosis of diffuse degeneration of the cord was made. The patient remained bedridden, with a stationary neurological picture. Finally she deteriorated mentally and died of inanition 6 years after the onset of her illness.

Necropsy Findings, Gross: The organs were small, but otherwise normal. The brain was normal on gross examination except for a few petechial hemorrhages in the hypothalamus, the midbrain and the floor of the 4th ventricle. The spinal cord in its upper half of the thoracic region was grayish, small and soft. The meninges of the ventral surface were thickened. On section, the gray and white matter were poorly defined. Otherwise the cord and its coverings appeared normal.

Microscopic Observations: The nerve cells of the frontal cortex and the hypothalamus showed slight degenerative changes. The pituitary gland was normal. The atrophied portion

* From the Division of Neuropathology, Pathology Department, University of Toronto, Canada.
of the spinal cord was diffusely infiltrated by granulomatous nodules, consisting of epithelioid cells, lymphocytes and giant cells (fig. 1). These were always associated with a vessel, the lesions arising in the perivascular spaces and spreading from there into the parenchyma of the cord. Sometimes only lymphocytic cuffing was evident. This was seen especially at the upper and lower limits of the involved region of the cord. The subarachnoid space covering the diseased portion was slightly infiltrated by lymphocytes. A few granulomatous nodules were attached to the adventitia of small meningeal vessels and one was situated in a dorsal nerve root. Neither necrosis nor tubercle bacilli were seen. Silver stains demonstrated reticulin in the older, well formed nodules. This reticulin was derived from the adventitia of the vessels and was at first laid down as a fine meshwork of fibres, which in the older lesions became thicker and coarser. In the segments of the cord, which were worst affected, all nerve cells were destroyed and Smith and Quigley stains demonstrated nearly complete demyelination. Towards the margins of the lesion, nerve cells and myelin sheaths were present between the granulomatous nodules. There was ascending degeneration of the long tracts above the diseased portion and descending degeneration below. Despite the fact that the condition was clinically stationary for over five years, the lesions were active throughout and failed to show any evidence of healing.

**Case 2. History:** A young man (C. K., NP: 406/45) who had been well except for a duodenal ulcer, developed diabetes insipidus at the age of 30 years. This was satisfactorily controlled by drugs. About 4½ years later, he noticed aching pains in the legs and loss of libido. His legs gradually became so weak that he could hardly walk. The polyuria recurred. On admission to the hospital, he was found to have an eunuchoid body build and hair distribution, an incomplete bitemporal hemianopia and areas of hyperaesthesia over the legs. He was emotionally unstable and, while in the hospital, deteriorated mentally. The cerebrospinal fluid contained 100 mg. per cent of protein. Five years after the onset of symptoms he suddenly lapsed into coma. The cerebrospinal fluid contained 500 mg. per cent of protein. He died the same day.

**Necropsy Findings, Gross:** The lungs and mediastinal lymph nodes contained active sarcoid lesions. The testes were atrophied. The spinal cord was normal. The pituitary gland weighed
0.6 Gm. and appeared normal. The brain weighed 1360 Gm. The floor of the 3rd ventricle was firm and brownish and the left optic nerve and tract were swollen. On sagittal section, a grayish mass stretched from the enlarged optic chiasma along the floor of the 3rd ventricle to the mammillary bodies and extended about half way up the lateral walls of the ventricle (fig. 2).

Microscopic Observations: The mass along the floor of the 3rd ventricle consisted of diffuse granulomatous tissue, composed of epithelioid cells, lymphocytes, plasma cells, a few eosinophiles and a very occasional small multinucleated giant cell. No necrosis was present nor were acid-fast bacteria demonstrable. In the lesion the capillaries had proliferated tremendously and argyrophilic reticulin spread out from their walls (fig. 3). This reticulin was not present everywhere in the lesion and was found more often in areas of purely lymphocytic proliferation than where epithelioid cells were present. At the margins of the lesion the Virchow-Robin spaces were filled with round and epithelioid cells. Scattered throughout the granulomatous mass and at its margin there were numerous hypertrophied, reacting astrocytes. The lesion extended into the subependymal region of the 3rd ventricle, but the ependyma itself was intact. The posterior half of the optic chiasma was invaded and partially demyelinated.

In the pituitary gland only a small area of fibrosis could be found in the pars intermedia. This was interpreted as a healed sarcoid lesion. The acidophilic cells of the anterior lobe were small and contained few granules.

Case 3. History: A woman, aged 42 years (I. T., NP: 583/48), developed progressive weakness and fatigue. Seven months later an orthodiagram and a chest plate were normal, but the patient was found to be anemic. She gradually deteriorated and died, one year after the onset of her illness.

Necropsy Findings, Gross: Nearly all viscera contained active sarcoid lesions. Death was due to diffuse sarcoidosis of the myocardium. The brain and spinal cord appeared normal and were not sectioned. The pituitary gland weighed 0.6 Gm. and was not remarkable.

Microscopic Observations: All parts of the pituitary gland were studded by small, circumscribed granulomatous nodules. These were most numerous in the pars intermedia. In the
Sarcoïdosis of Central Nervous System

In the anterior lobe they were round, and consisted mostly of epithelioid cells with some giant cells (fig. 4). No inclusion bodies were present. In the posterior lobe the nodules were ovoid in

![Figure 3](case2_hypothalamus.png)

**FIG. 3, (Case 2.)** Right Hypothalamus.

Argyrophilic reticulin spreading out from the wall of a capillary. Laidlaw's silver stain, X 320.

![Figure 4](case3_pituitary.png)

**FIG. 4, (Case 3.)** Pituitary Gland.

A round nodule in the anterior lobe, consisting of epithelioid cells, a few lymphocytes and a multinucleated giant cell. Hematoxylin and eosin stain, X 296.

Neither necrosis nor acid-fast bacteria were demonstrable.

**Case 4. History:** A young man, aged 23 years (S. L., NP: 434/45), developed left-sided
Jacksonian epilepsy. These attacks began in the left hand and spread to the left leg. Six years after the onset of his illness, ventriculography and an exploratory right craniotomy failed to reveal anything abnormal. During the next 3 years the seizures became so severe that they could not be controlled by drugs. The left arm and leg had gradually become paralyzed. A ventriculogram now showed a depression of the roof of the whole right lateral ventricle.

A bone flap was turned down by Dr. C. P. McCormick. Areas resembling cortical scars, distinct from the old needle puncture wounds, were found in the arm area of the right pre- and post-central gyri. Multiple small translucent blue-gray nodules, 1–2 mm. in diameter, were seen at the lower end of the falx cerebri. They did not appear to invade the underlying corpus callosum. The scarred areas were excised and as many of the nodules as possible removed.

![Figure 5](Case 4. Biopsy)

The meninges are filled with granulomatous nodules. Invasion of cerebral cortex is seen in the lower half of the photograph. Hematoxylin and eosin stain, X 41.

**Biopsy Studies:** The leptomeninges contained numerous well circumscribed, round, granulomatous nodules, surrounded by dense mantles of lymphocytes, and the underlying cortex was invaded (fig. 5). A few of the larger nodules had degenerate, fibrillary centres. No tubercle bacilli could be demonstrated in the lesions.

**Course:** Following the operation, the patient retained an incomplete left spastic hemiplegia. He still had Jacksonian attacks, but these were mild and infrequent, and could be controlled by drugs. When last seen, 5 years after the operation and 14 years after the onset of symptoms, he was unchanged except for a slight increase in the frequency of seizures. He has at no time shown any clinical evidence of sarcoidosis elsewhere in the body.

**Case 5. History:** A woman aged 41 years (M. B., NP: 19/41), presented herself with primary optic atrophy and a bitemporal field defect. Language difficulties made history-taking impossible. Since x-ray studies of the skull showed a normal sella turcica, a meningioma was diagnosed. There was no evidence of extracranial disease.

At operation the intracranial portions of the optic nerves were found by Dr. K. G. McKenzie to be swollen to about 4 times their normal size and were grayish in color. The chiasma was enlarged and a projection of tumor extended into the floor of the 3rd ventricle. It was thought to be an inoperable tumor of the optic chiasma and only a biopsy was taken. The subsequent history of this case is not known.
Microscopic Observations: The optic chiasma contained typical granulomatous nodules of epithelioid cells, round cells and occasional giant cells. The surrounding tissue was gliosed, containing numerous hypertrophied astrocytes and glial fibres. No necrosis or acid-fast bacteria were seen.

Discussion

An analysis of the foregoing cases and those cases collected from the literature, which include histological findings (6-16), demonstrates the following points. The age at the onset of symptoms varies considerably, the youngest being reported by Naumann (12) in a child of 3 months, the oldest being one of our cases, a woman of 53 years. Generally it is a disease of young people in the 3rd or 4th decade of life, the average age of onset among 16 cases being 29 years. The distribution among the sexes is approximately equal.

The symptomatology is extremely variable, depending on the site of the lesions in the brain, and the correct diagnosis is therefore seldom made clinically. Sarcoidosis is most frequently mistaken for intracranial tumour, but Naumann's case (12) resembled meningitis, and a diagnosis of disseminated sclerosis was made in Zollinger's (13) patient. Involvement of the pituitary gland and hypothalamus may cause diabetes insipidus and endocrine disturbances (7, 10, 11, 15, 16 and Case 2). The course of the disease also does not conform to any uniform pattern. It may run a benign, self-limiting course, have remissions and exacerbations (13), remain stationary for years, run a progressively declining course or cause sudden death (14). Usually, however, it is a chronic condition, lasting for months or years before recovery or a fatal termination. In those cases in which the cerebrospinal fluid was examined, the protein content was elevated and the cells were slightly increased in number. These findings are, however, unspecific, and the clinical diagnosis, therefore, is usually based on the proof of sarcoidosis elsewhere in the body by biopsy of affected skin or lymph nodes. Extracranial lesions are nearly always present. In only 2 out of the 13 fatal cases reported here and in the literature was the disease confined to the nervous system and it is quite possible that small lesions were overlooked. Since the extracranial lesions may be subclinical, a certain percentage of cases remains, in which the diagnosis cannot be made during life. In none of the cases reported here, with the exception of those in which biopsies were taken, was the diagnosis made clinically.

Sarcoidosis may occur anywhere in the brain and spinal cord. Most commonly the meninges and the region of the floor of the 3rd ventricle, including the optic nerves and pituitary gland, are affected. These areas were involved in 15 out of 17 cases. Roos (17) in a clinical analysis of a series of cases found a similar distribution. The spinal cord is only rarely the seat of the disease. Reisner (18) reported a patient with symptoms of damage to the lower segments of the spinal cord and in Erickson's case (15) the spinal cord was slightly invaded from the meninges. In our case (Case 1) the spinal cord appeared to be primarily affected, the adjacent meninges being so slightly infiltrated as to suggest a secondary extension.

The gross appearance of the lesions is variable. The infiltration may be so
diffuse or slight that nothing abnormal is seen. Often the lesions are gray, firm, infiltrating masses and are mistaken for tumor. Occasionally an adhesive arachnoiditis is present or simple atrophy is simulated.

Microscopically the lesions are similar to those seen elsewhere in the body, consisting of epithelioid cells, lymphocytes, giant cells and occasionally plasma cells. Polymorphonuclear leukocytes are never seen, but in one of our cases (Case 2), eosinophils were present. Giant cells tend to be small and scarce in the nervous tissue. In none of our cases were inclusion bodies encountered. The lesions in the anterior and posterior lobe of the pituitary gland in Case 3 merit comparison. In the epithelial part of the gland well defined round nodules were formed, consisting mainly of epithelioid cells and giant cells, while the lesions in the pars nervosa were much smaller and elliptical, consisting chiefly of lymphocytes and without any giant cells. The shape of the lesions in the posterior lobe may have been due to the compressing effect of the nerve and glial fibres. Only 1 case (Case 4) contained central areas of degeneration. These, however, were not true necrosis and did not resemble caseation, but appeared to be a loss of cells with retention of the fibrillary background. Reticulin stains were unfortunately not available on this case. The lesions usually consisted of a conglomerate of nodules, but occasionally a diffuse granuloma was formed (Case 2), a phenomenon met with otherwise only in sarcoidosis of the heart. Perhaps the structure of nervous tissue and myocardium, consisting essentially of a loose meshwork of fibres, lends itself more readily to a diffuse spreading of the cells along the natural lines of cleavage.

It is not known by what route the nervous system becomes infected—if indeed infection it is. The high incidence of sarcoidosis in the eye and the hypothalamic region points, perhaps, to a direct extension from the orbit. Where other parts of the brain or the spinal cord are involved, a blood stream infection seems more likely. The spread of the disease in brain tissue is by the perivascular spaces. This was well demonstrated in Zollinger's (13) case, in which the lesions were confined to the Virchow-Robin spaces throughout the brain.

The histological structure of the lesions is dependent upon a close association with vessels, as it is in extracranial sarcoidosis. The reticulin framework, foreign to nervous tissue, is derived from the capillary walls. Of the cellular elements certainly the lymphocytes must come from the blood stream and it is possible that the epithelioid cells have the same source. Since the latter probably stem from the reticulo-endothelial system, one must also consider the possibility that they develop in the brain from the system's native representatives there, the microglia cells. Sections from Cases 1 and 2, however, stained with the Cone and Penfield modification of the silver carbonate stain, failed to demonstrate any increase in the number of microglia cells or any relationship between them and the epithelioid cells. It is interesting to note that no evidence was found that epithelioid cells are concerned with the production of reticulin, the latter occurring also in areas of purely lymphocytic proliferation.

The lesions produce localized destruction of the nervous tissue, which may lead to secondary degeneration of nerve tracts. The adjacent nerve tissue reacts to the irritation by gliosis, as indicated by a proliferation of hypertrophied astrocytes.
SARCOIDOSIS OF CENTRAL NERVOUS SYSTEM

and glial fibres. An excessive production of collagen was seen only in those areas where it occurs naturally, such as in the meninges or the pituitary gland.

The natural history of the disease in the brain serves to differentiate it sharply from tuberculosis and may help to shed light on its etiology. While both diseases have a predilection for the meninges and the base of the brain, direct massive invasion of the brain from the subarachnoid space is seen much more commonly in sarcoidosis. The frequently benign and self-limited course of sarcoidosis, its inability to produce a definite meningitis and therefore its failure to be activated by operative interference are points in which sarcoidosis differs radically from the behavior of a tuberculous infection. One of Colover's (6) patients, who was observed for 3 months after operation, and one of ours (Case 4) who has been followed up for 5 years, were definitely improved by surgical treatment. As long as no medical therapy of the disease is available, surgical treatment is indicated and holds hope for patients with sarcoid lesions in accessible parts of the brain.

SUMMARY

Five cases of sarcoidosis of the central nervous system with histological findings are described together with 12 similar cases assembled from the literature. The histology of the lesions in the brain and the natural history of the disease are discussed.

I wish to express my gratitude to Dr. E. A. Linell for his advice and encouragement and the permission to use the cases from the files of the Neuropathology Department.

I am indebted to Dr. K. G. McKenzie and Dr. C. P. McCormick for the histories and specimens of the two surgical cases.

REFERENCES