Noninfectious granulomatous angiitis with a predilection for the nervous system

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THE CENTRAL NERVOUS SYSTEM is only rarely affected in patients with most forms of non-infectious angiitis. In a small proportion of patients with periarteritis nodosa, the vessels of the nervous system alter as do other organs and cause hemorrhage and/or ischemic changes in the brain with neurologic signs and symptoms.¹⁻³

In pulseless disease,⁴ temporal arteritis,⁵⁻⁷ giant cell arteritis,^{8,9} and thromboangiitis obliterans,¹⁰ the vessels of the nervous system generally escape direct involvement. However, in a few patients, pathologic changes in the great vessels of the neck induce neurologic manifestations which indicate ischemic changes in the brain.

Apparently a specific form of angiitis, generally designated as granulomatous angiitis, regularly affects the vessels of the central nervous system, at times without concurrent involvement of other organs, at times involving other organs to a less significant degree. In these patients, the clinical symptomatology is essentially neurologic; involvement of other organs, when present, generally escapes clinical attention. Cases which we believe to be of this type have been described previously by Harbits,¹¹ Newman and Wolf,¹² Richardson,¹³ and McCormick and Neuburger,¹⁴ although, in some of these, other interpretations have been offered. The purpose of this paper is to present detailed observations of 2 additional cases of this nature and to suggest that the group warrants consideration as a separate clinicopathologic entity.

CASE REPORTS

Case 1. A 56-year-old woman was admitted to the hospital on October 3, 1956, because of an episode of aphasia followed by convulsive

movements of the right side of the face and the right arm.

Except for the usual childhood diseases, she had not previously been ill. Onset of symptoms began early in November 1954 when she had persistent vomiting associated with frontal headaches. Physical examination at that time showed a normal blood pressure, papilledema on the right, optic atrophy on the left, a positive Romberg's sign, and normal cerebrospinal fluid. Skull x-rays showed a calcification of the posterior clinoid processes and what was thought to be a posterior displacement of a calcified pineal gland. A ventriculogram and a pneumoencephalogram revealed a normal ventricular system.

The patient left the hospital against medical advice about a month after admission. Approximately one year later, she had a second transient episode of aphasia and a sudden episode of loss of consciousness lasting thirty minutes. Examination at this time showed a visual acuity of 20/20 on the right and 20/70 on the left (corrected). The visual fields were normal; neither papilledema nor atrophy of the optic disks was observed. She continued to have intermittent episodes of headache and vomiting. In June 1956, she developed progressive weakness of both legs and had frequent falls without loss of consciousness. During the following month, she began to show gradual mental deterioration

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which was evidenced by loss of memory, disorientation, and confusion. On October 3, 1956, she had a right-sided convulsive seizure and was admitted to the hospital for the last time.

Physical examination revealed the blood pressure to be 150/80; the pulse, 78 and regular; the respiratory rate, 18; and the temperature, 100.2° F. The patient appeared disoriented for time and place, demonstrated a childish, irrational behavior, and was occasionally belligerent. She had marked memory loss, a poor capacity for calculation, and difficulty in naming objects and recognizing printed letters. Visual acuity was extremely decreased in the left eye to 20/200; she had disk pallor and a concentric constriction of the right visual field with blurring of the right optic disk. The other cranial nerve functions appeared normal. The patient had slight weakness and increased deep tendon reflexes of the right extremities, a right Babinski sign, and bilateral Hoffmann reflexes. All modalities of sensation appeared normal. No abnormalities were recognized with respect to the other organ systems.

The blood count and urinalysis and determinations for blood urea nitrogen, fasting blood sugar, serum proteins, cholesterol, cholesterol esters, serum sodium, potassium, chlorides, calcium, and phosphorous revealed normal values. Wassermann reaction was negative. The erythrocyte sedimentation rate was 35 mm. per hour. The cerebrospinal fluid examination revealed 62 red blood cells per cubic millimeter, half of them crenated; 3 lymphocytes per cubic millimeter; 88 mg. per cent of protein; a negative Wassermann reaction and colloidal gold curve; and a pressure of 220 mm. of water. The x-rays of the skull showed a questionable deepening of the floor of the sella turcica, with slight atrophy of the posterior clinoid processes, and an old post-operative defect in the right parietooccipital region. The x-ray of the chest was normal. The electroencephalogram revealed slow, 5 to 6 per second, high voltage activity in both frontal regions. The record was considered to show a diffuse abnormality more marked on the right but with no focal accentuation.

The patient became progressively lethargic, was soon unable to feed herself, and de-

veloped a frank right hemiparesis. Vomiting and headaches were not observed during the first three weeks of hospitalization. However, on October 24, she at first vomited food and, later, what appeared to be gross blood. On October 30, she had severe convulsive movements of the face and left leg and smacking movements of the lips. The movements were controlled with intravenous amobarbital sodium. A lumbar puncture disclosed a slightly xanthochromic spinal fluid under a pressure of 180 mm. of water, a protein content of 57 mg. per cent, and 363 fresh red blood cells per cubic millimeter.

The following day, the severe convulsive movements recurred and she was given intravenous and intramuscular phenobarbital sodium. The convulsive seizures were at first markedly reduced, but, after one hour, frequency increased. At this time, 0.75 cc. of paraldehyde was given intravenously without effect. She received intravenous amobarbital sodium two hours later with some, but not complete, relief of the seizures. About thirty minutes later, she suddenly became apneic and died.

At autopsy, the brain weighed 1,100 gm. Externally, the brain appeared normal except for the thickened milky appearance of the leptomeninges, particularly at the base. The left optic nerve was slightly smaller than the right. The upper 3 cervical segments of the spinal cord were available and appeared externally normal. Coronal sections revealed a fresh linear hemorrhage in the middle part of the right anterior commissure measuring 10 x 3 x 3 mm. The ventricular system was minimally dilated. The ventricular lining appeared rough and coarsely granular, particularly in the frontal horns. No other grossly pathologic changes were evident.

Microscopically, a severe granulomatous process involved arteries and veins of varying caliber, from the middle cerebral artery to the intraparenchymal vessels (Figs. 1, 2, and 3) in nearly every portion of the central nervous tissues studied. The lesions were characterized by a proliferation of connective tissue fibers and of mononuclear mesenchymal cells of varying types, including fibroblasts, lymphocytes, large mononuclear cells, and multinucleated giant cells of both the foreign body and Langhans' type (Fig. 2).

Fig. 1. Case 1. The lumen is markedly narrowed by a thickened and infiltrated intima containing a great many large mononuclear cells, many fibroblasts, many lymphocytes, and a few giant cells. The adventitial infiltrate is largely lymphocytic. (Hematoxylin and eosin $\times 250$)

The process involved the entire thickness of the walls of some vessels, but the intimal and adventitial tissues were often more severely affected than the media, which was often spared. The intimal involvement was particularly severe in the intraparenchymal vessels, where the large mononuclear cells and giant cells were particularly abundant.

In the intraparenchymal vessels, the adventitial tissues tended to contain large numbers of lymphocytes, although large mononuclear cells and giant cells were also present. The large leptomeningeal arteries were less affected than the smaller leptomeningeal vessels and

revealed a comparatively modest adventitial involvement, often with large mononuclear and giant cells predominating. The smaller leptomeningeal arteries resembled those within the brain substance. The veins were affected (Fig. 2) but, apparently, with lesser frequency than the arteries. An adventitial and perivascular granulomatous infiltration was often noted. However, it was frequently impossible to decide whether a markedly affected vessel was a vein or an artery.

Fibrinoid changes were present but in only a few of the altered vessels. The lumens of the affected vessels were often markedly

Fig. 2. Case 1. Leptomeningeal vein in cerebrium revealing a focal granuloma with a giant cell of Langhans' type. (Hematoxylin and eosin $\times 600$)

Fig. 3. Case 1. Intraparenchymal vessel with thickened granulomatous wall and narrow lumen. (Hematoxylin and eosin $\times 800$)

narrowed or completely occluded (Fig. 3). The process was particularly severe in the leptomeninges, the subependymal white matter of the cerebrum, the tegmentum of the brain stem, and in the cerebellum; but no portion of the central nervous tissues was spared.

Lesions were observed in the sixth cranial nerve and in the optic chiasm. The cerebellum revealed a large, focal, old, cystic infarct (Fig. 4), and additional areas demonstrated a loss of Purkinje and granular cells and a proliferation of Bergmann astrocytes. Typical fresh infarcts were not noted in the cerebrum, brain

stem, or cord, but many areas within these structures appeared rarefied; showed non-specific neuronal changes, including rare necrotic neurons and moderate neuron loss; and had a marked, reactive astrocytosis. These are probably ischemic changes. The hemorrhage in the anterior commissure was recent. No fungi, tubercle bacilli, or other bacteria were demonstrated with special staining procedures.

Study of the other organs revealed no lesions resembling those in the brain. The only abnormalities noted were an old renal infarct, pulmonary edema, and the presence of emboli

Fig. 4. Case 1. Old cerebellar infarct. (Hematoxylin and eosin $\times 75$)

in some small branches of the pulmonary artery.

Case 2. The patient, an 18-year-old youth, was admitted to the hospital for the third time on June 2, 1953, nineteen days prior to his death. He had numbness of the left side of the body and speech difficulties. The patient had had diabetes mellitus since 1940, when he came to the hospital because of weight loss, polyuria, and polydipsia. He was discharged on a special diet and told to take 10 units of protamin-zinc-insulin daily. In 1945, he was admitted a second time for diarrhea of undetermined origin which subsided during hospitalization. At that time, his diabetes was well controlled, although the dosage of insulin had gradually been increased from 10 to 85 units daily. For much of his life, he presented a problem of disorderly behavior and lived in a poor social environment.

During the first week of May 1953, about six weeks prior to his death, he began to complain of left temporal headaches and appeared to his family to be less alert than usual. By the end of the month, he had become drowsy and complained of progressive generalized weakness and stiffness and numbness of his left extremities. By June 1, 1953, he had developed horizontal diplopia for distant objects which was more pronounced on right lateral gaze and numbness of the left side of his face. The following day his voice became weak, and he was hospitalized.

On admission, his blood pressure was 140/90; pulse rate, 128 per minute; and temperature, 99° F. He appeared drowsy and was slightly disoriented for time.

The optic fundi and the visual fields were normal. The pupils appeared normal in size and shape and reacted well to light. He had slight ptosis of the right eyelid and a horizontal diplopia on right lateral gaze but no gross weakness of gaze or of individual eye muscles. Unsustained nystagmus was noted on right lateral and upward gazes. A mild left hemiparesis involving the arm, leg, and face, in approximately that order of severity, was also noted. The distal segments of the limbs appeared weaker than the proximal. The left biceps jerk was greater than the right. Both knee jerks were absent. The right ankle jerk was depressed, while the left appeared absent.

There was a left Babinski sign. All modalities of sensation with both single and double simultaneous stimuli appeared normal.

A complete blood count was normal. The erythrocyte sedimentation rate was 27 mm. per hour. Examination of the urine revealed a specific gravity of 1.010, 2+ sugar, no acetone or diacetic acid, and 2 to 3 red blood cells per high-power field. The blood Wassermann was negative. The fasting blood sugar was 420 mg. per cent. The blood urea nitrogen, carbon dioxide combining power, serum electrolytes, serum proteins, and cholesterol and its esters were of normal value. The cerebrospinal fluid pressure was 180 mm. of water. The spinal fluid contained 2 lymphocytes per cubic millimeter, 17 mg. per cent protein, and 98 mg. per cent sugar. The spinal fluid Wassermann and colloidal gold curve were negative. The skull and chest x-rays were normal. The electroencephalogram was considered diffusely abnormal—showing low voltage slow activity accentuated posteriorly—more so on the right side.

Approximately one month after onset and fourteen days before death, the patient complained of blurred vision and his diplopia became prominent in all directions of gaze. Nystagmus on left and upward lateral gazes was also noted. At this time, however, his hemiparesis had improved. Amobarbital sodium (0.4 gm.) was given intravenously and produced severe disorientation, confabulation, and denial of illness which suggested diffuse cerebral dysfunction.

The patient had become increasingly depressed and lethargic and showed severe dysphagia and dysarthria eight days prior to death. The right palpebral fissure was greater than the left. He had marked palatopharyngeal paresis, absence of the gag reflex, dysphonia, and a high-pitched voice. He was unable to protrude his tongue easily. In addition to the hypertonic left hemiparesis, he had some weakness of the right upper extremity. Sensation remained intact. During the last seven days of his life, the disease progressed very rapidly. Bilateral palpebral ptosis, a sensory deficit over the right lower extremity, bilateral Babinski signs, diplegia which rapidly evolved to quadriplegia, palatoplegia, and weakness of the jaw and facial

Fig. 5. Case 2. Middle cerebral artery. An eccentric granulomatous plaque in the intima is composed of large mononuclear cells, lymphocytes, and multinucleated giant cells of a foreign body type. The lumen is narrowed. The elastica and media are normal. The adventitia is infiltrated by lymphocytes.

musculature were apparent. An adequate airway became difficult to maintain. The patient became comatose, his blood pressure rose to 160/70, his temperature to 106° F., and he died on the twentieth hospital day.

At autopsy, the brain weighed 1,200 gm. No external abnormalities were found except for an unusual opacity of some of the large arteries, particularly the anterior spinal artery. Leptomeningeal congestion was also seen. Coronal sections revealed areas of infarction involving the right occipital lobe, the left temporoparietal area of the cerebrum, and the left side of the base of the midpons and medulla. These lesions were soft, dusky, and irregular in contour; those in the cerebrum revealed an obscuration of the corticomedullary junction. No other gross changes were recognized.

Microscopically, the areas of infarction revealed the characteristic rarefaction, parenchymal disruption, punctate hemorrhages, focal infiltration of polymorphonuclear leukocytes, and more marked and more widespread proliferation of microglial phagocytes and homogenizing necrosis of neurons.

The primary changes were in the walls of the blood vessels and resembled the changes described in Case 1 (Figs. 5, 6, and 7). A

striking characteristic in this instance was the localization of the process to the intima of major vessels, such as the middle cerebral artery (Fig. 5) where it formed a sharply localized projection into the lumen which caused narrowing. Some of the arteries were occluded by bland thrombotic material, and, in some instances, giant cells and mononuclear cells indicated that an intimal granuloma was the site of the thrombosis. A few granulomas of like character were present in the dura. In other respects, the microscopic changes in the brain were like those described for Case 1 (Figs. 6 and 7).

The lungs revealed a severe lobular pneumonia, thromboembolic material in some of the vessels, and small granulomas like those in the brain about some of the smaller arteries. The heart had numerous granulomata around the epicardial vessels, within the endocardium, in the myocardium, in the intima of the aorta and pulmonary artery, and in the media of the pulmonary artery. Thrombotic material was present over the lesions in the pulmonary artery. Lymphocytes extended from the focal myocardial lesions into the adjacent interstitial tissues. Granulomas of such character were present in the lymph nodes, spleen, serosa of the stomach, and the liver. In the liver, some of the lesions were characterized by central necrosis surrounded by mononuclear cells in a palisading fashion. The kidney revealed a gross infarct and hyaline arteriolar changes, some of which extended into the glomeruli. Fungi, tubercle bacilli, and other bacteria were not demonstrable with special staining techniques.

DISCUSSION

Our opinion is that the 2 cases described here and the other 6 collected from the literature (see table)* should be grouped together as delineating a distinct clinical and pathologic entity which may be designated noninfectious granulomatous angiitis with a predilection for the nervous system. It is recognized that the delineation of such an entity within the group of diseases characterized by a generalized noninfectious arteritis must be considered tentative until the etiology and pathogenesis of the various forms of these types of angiitides are

*See also footnote at end of article.

established. Nevertheless, the pattern of the disease process here described does appear to segregate this form from the other forms of noninfectious arteritis.

Perhaps the most striking point of distinction is that, in each of the patients considered in this paper, the disease process involved the central nervous system predominantly. In 4 patients no concomitant involvement of any other organ of the body occurred, while, in 2 patients, such visceral involvement was present, although less extensive and less severe. In 2 patients, autopsy was limited to the central nervous system. In all 8, the clinical features were essentially neurologic; no clear clinical evidence of the visceral involvement was found, even in the 2 patients in whom such involvement was demonstrated pathologically. The nature of the essentially granulomatous process serves as another feature common to the cases enumerated and distinguishable from the other forms of arteritis.

Pulseless disease (Takayasu)^{4,5} appears to be a clinical syndrome frequently affecting young women and is due to involvement of the major branches of the arch of the aorta, such as the subclavian or the carotid arteries, by granulomatous processes of various types, some of which are clearly luetic. When central nervous system involvement in pulseless disease does occur, it is the result of narrowing of the carotid arteries in the neck. No patient, to the best of our knowledge, has shown evidence of involvement of the intracerebral vasculature.

The involvement of the intracranial arteries by thromboangiitis obliterans (Buerger's disease), has been considered frequent by some¹⁶ and nonexistent by others.¹⁷ In a report describing this condition in the nervous system,¹⁸ it is stated that the lesions bear no histologic resemblance to the lesions which characteristically involve the vessels of the extremities in thromboangiitis obliterans and that the process may be limited to the vessels of the nervous system. In these circumstances, the identity of the cerebral process described with the characteristic thromboangiitis obliterans of the extremities may be considered uncertain.

In temporal arteritis (cranial arteritis, giant cell arteritis), the temporal artery alone is involved in most instances,^{5,19,20} although some-

Fig. 6. Case 2. Leptomeningeal vessel about medulla. The lumen is almost completely obliterated by a cellular granulation tissue containing multinucleated giant cells of the foreign body type; 2 adventitial granulomas are present as well. (Hematoxylin and eosin $\times 400$)

Fig. 7. Case 2. Leptomeningeal vessel about medulla. The lumen is almost completely filled as a result of a marked cellular proliferation in the intima. A Langhans' giant cell is present. The media is relatively preserved. (Hematoxylin and eosin $\times 500$)

times other branches of the aorta are involved as well.^{9,21} The temporal artery is spared in some cases.⁸ Involvement of the nervous system is rare, and, when it does occur, it is generally due to involvement of the common or

Case:	1	2	Harbitts ¹¹	Newman & Wolf Case 1 ¹²	Newman & Wolf Case 2 ¹²	Richardson ¹³	McCormick & Neuburger Case 1 ¹⁴	McCormick & Neuburger Case 2 ¹⁴
Age	18	56	26	middle-aged	elderly	64	50	55
Sex	M	F	F	M	M	M	F	F
Duration	6 weeks	2½ years	2 years	6 weeks	2½ years	5 weeks	9½ months	3 days
Hypertension	0	0	0	0	0	0	0	0
Allergy	0	0	0	0	Asthma	0	0	0
Headache	•	•	•	•	•	•	•	•
Convulsions	•	0	•	0	0	•	•	•
Stupor-Coma	•	•	•	0	0	•	•	•
Multifocal CNS signs	•	•	•	•	•	•	•	•
Remissions	•	0	•	0	•	0	•	0
CSF protein (mg. %)	88	17	•	•	100	62	92	130
CSF lymphocytes	3	2	•	•	55-432	49	40	55
EEG abnormality	diffuse	diffuse	•	•	•	diffuse	•	•
Other viscera	•	0	•	•	•	0	0	0

• indicates the known presence and 0 indicates the known absence of the feature indicated. A blank space indicates the absence of data. The heading, Other viscera, indicates the presence or absence of lesions in other viscera as disclosed by autopsy.

internal carotid arteries with consequent narrowing and occlusion or occasionally with the formation of thromboemboli. The number of cases in which the intracranial vessels are reported to have been involved is very small and, in some of these reports,^{22,23} pathologic data is incomplete. Temporal arteritis is an entity which characteristically affects elderly people and appears generally to be a self-limited, nonfatal process. Temporal arteritis takes the form of a granulomatous panarteritis predominantly affecting the media and associated with necrosis and thrombosis. The media is often spared in granulomatous angiitis. When the process affects the carotid arteries, carotid insufficiency or occlusion may result and death may occur.^{6,21}

Cases 7 and 8 in the group of granulomatous angiitis of the nervous system were interpreted by those reporting them¹⁴ as giant cell arteritis (temporal arteritis). In the light of the skill and experience of those making the report, we are naturally hesitant to offer an alternative interpretation. However, we are encouraged to do so by their stated opinion that the involvement of the small meningeal and intracerebral vessels in these patients seems unique among cases of temporal arteritis. The similarity of these 2 patients to the others listed in the table appears to us to be much greater than their resemblance to temporal arteritis. In both, the temporal arteries were spared, while the predilection for the nervous system was very marked. There was only mural thickening of the left subclavian and axillary arteries in 1 patient, and no extracranial involvement in the other.

Periarteritis nodosa may be distinguished by the infrequent involvement of the brain, even in cases of widespread visceral involvement.^{1,24} When the cerebral vessels are involved, a fibrinoid alteration is prominent, a change which is rather infrequent and not intense in granulomatous angiitis of the nervous system. Granulomatous changes in periarteritis nodosa are much less marked. Hypersensitivity angiitis, which some would distinguish from periarteritis nodosa with which it has been grouped, is described in many reports as a rapidly fatal process. Hypersensitivity angiitis is assumed to be a manifestation of

allergy, often to sulfonamides or other substances.^{25,26}

Pathologically, the resemblance of the lesions of granulomatous angiitis of the nervous system to those reported as allergic granulomatosis²⁷ is noteworthy. As reported by Churg and Strauss,²⁷ this condition is invariably associated with bronchial asthma, and the arteritis is assumed to be a manifestation of hypersensitivity. As can be seen in the table, asthma was present in only 1 of the patients grouped as granulomatous angiitis. One of us (I.F.) has had occasion to examine the 4 available brains of the original Churg and Strauss series of allergic granulomatosis. None of these brains showed vascular lesions comparable to those present in the viscera and skin. On the other hand, Dr. Strauss had an opportunity to examine the second case of the present report and expressed the opinion that the lesions were not precisely identical to those in the cases she had originally reported as allergic granulomatosis. Nevertheless, the lesions in these 2 processes are so similar that Newman and Wolf¹² appear entirely justified in calling attention to the resemblance of the lesions in their 2 patients (Cases 3 and 4 of the table) to those of allergic granulomatosis, particularly since 1 of their patients had had bronchial asthma and the other a dermatitis that could have been allergic in nature.

Sarcoidosis (Boeck) of the central nervous system is quite rare²⁸ and generally assumes the form of a diffuse granulomatous leptomeningitis or less often, of circumscribed large granulomas within the brain substance.^{29,30} Evidence is usually found of involvement of other viscera as well.²⁸ In general, this disease of connective tissues does not primarily involve blood vessels. In the leptomeninges, and, certainly, within the brain substances, the lesions—if small enough—would lie in relation to the walls of blood vessels, the major sources of connective tissues in the brain. Some of these lesions may resemble the lesions of the granulomatous angiitis of the nervous system.³⁰ None of the more common lesions of sarcoid were present in the cases listed in the table.

A form of cerebral hyalinosis exists which affects the cerebral arteries of hypertensive patients and which may be the basis for the

cerebral hemorrhage noted in this connection.³¹ However, such lesions are less frequent, show much more fibrinoid change and greater inflammatory reaction, and appear uniformly associated with hypertension. This seems to be the only other arteritic process, apart from the disease entity suggested here, which shows a predilection for involvement of the central nervous system.

The cases listed in the table reveal a disease pattern different from the other arteritic processes just enumerated. They show a predominant and often exclusive involvement of the vessels of the central nervous system by a severe, widespread, granulomatous inflammation. The inflammatory infiltrate contains many lymphocytes and fibroblasts, a rare eosinophil, many giant cells of both the foreign body and the Langhans types, and a considerable deposition of connective tissue fibers.

The lumen of the vessels so affected appear markedly narrowed, and ischemic lesions are noted in the adjacent neural tissues. Rarely, small hemorrhages are also present. The granulomatous process sometimes involves the major intracranial vessels, but, more characteristically, the process involves the smaller meningeal and parenchymal vessels. The arteries are predominantly affected, although involvement of veins is also clearly present. The pathologic process may affect only the intima, this change being noted particularly in the large vessels. It may involve the intima and the adventitia, sparing the media. Most frequently, it affects the entire thickness of the vessel wall. The granulomatous process may be very extensive, and, at times, confluence of lesions in adjacent vessels is readily appreciated. Occasionally, the granulomatous lesions are noted in the meninges without obvious relationship to blood vessels. Visceral involvement, when it occurs, resembles the lesion in the nervous system, although occasionally there are large lesions of the extravascular tissues, such as the necrotic hepatic lesions noted in Case 2.

The nature of the granulomatous arteritis described here is no less obscure than that of the other forms of noninfectious arteritis previously discussed. The evidence for hypersensitivity states, so often implicated in these conditions, is largely inferential. In the cases of granulomatous angiitis cited, hypersensi-

tivity was not manifest in any consistent and clearly recognizable form. Arterial hypertension, implicated in some other forms of arteritis, was absent in most instances. Infectious agents, such as tubercle bacilli, fungi, and parasites, were not demonstrated. Indeed, we have not been able to recognize any factor which might suggest a pathogenic mechanism for this process. In this circumstance, the delineation of this entity by virtue of its specific involvement of central nervous tissues and its granulomatous character may be considered provisional.

Granulomatous angiitis of the nervous system affects individuals of all ages but perhaps most frequently affects those of middle age. In this series, the youngest patient was 18, the oldest, 64. Both sexes were equally affected. After onset, the disease was fatal in three days in 1 patient, in less than six weeks in 3 patients, and in two to two and one-half years in 4. In all patients, the clinical manifestations were referable to the nervous system. The symptomatology was that of a diffuse disorder of the central nervous system with some focal accentuation. In this series, the focal accentuation of symptoms indicated disease most marked in the cerebrum in 5 patients, in the brain stem in 1, and in the spinal cord in 2. The salient clinical features included headaches of intermittent nature, slight fever, organic mental syndrome, convulsive seizures, somnolence, and lethargy. In addition, there was frequent impairment of cranial nerve functions, speech disturbances, aphasia, hemiparesis, paraparesis, and various forms of sensory deficits. These manifestations varied from patient to patient according to the localization of the arteritic process. A slight to moderate leukocytosis was found in the peripheral blood. The cerebrospinal fluid usually contained an increase in protein and a moderate pleocytosis, usually of lymphocytes, and the fluid sometimes appeared xanthochromic. The electroencephalogram was usually diffusely abnormal. The pneumoencephalogram was normal in most patients or showed a slight dilation of the ventricular system in a few.

The disease has been confused with neoplasm, multiple sclerosis, and toxic or metabolic disorders. Because neoplasm was suspected, 3 of the 8 patients discussed here had

exploratory craniotomy with negative results.

The symptomatology of granulomatous angiitis of the nervous system is varied and confusing. Perhaps this process should be considered among the diagnostic possibilities in those patients in whom a protean neurologic symptomatology does not permit a definite diagnosis of a more common disease process. This possibility may warrant particular consideration in those obscure neurologic cases in which some of the clinical features suggest tumor. If a surgical exploration fails to disclose tumor, biopsy of nonneoplastic tissues might reveal the vascular lesions of this process and establish the diagnosis.

In regard to therapy, we have no specific suggestions to offer, except to recall that cortisone and ACTH have apparently effected improvement in some arteritic conditions of similar noninfectious character.

SUMMARY

Granulomatous alteration of the vessels of the central nervous system is described in 2 patients. In 1, the process was limited to the brain; in the other, visceral involvement was also present, although to a less significant degree. Attention was directed to the occurrence of 6 other cases found in the literature which resembled these patients clinically and pathologically. In all these patients, predominant and, at times, exclusive involvement was found of the vessels of the nervous system by a granulomatous angiitis which involved both arteries and veins—although the arterial lesions predominated.

The process essentially consisted of a proliferation of various mesenchymal cells in the intima, the adventitia, or in all layers of the vessel wall. Giant cells of the Langhans or foreign-body types were prominent among these infiltrating cells. The clinical picture was that of a nervous system disorder of a diffuse nature with some focal accentuation. In no instance was there clinical evidence of involvement of organs other than the nervous system. It is suggested that these cases warrant consideration as an entity, distinct from other forms of generalized arteritis, and that these be designated as granulomatous angiitis with a predilection for the central nervous system.

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FOOTNOTE

As this paper was being completed, we were given the opportunity of examining sections of a very similar case which will be reported separately by Dr. John Moosy of the Louisiana State University School of Medicine.

A 30-year-old woman died after an illness of approximately three months, during which time she experienced multiple episodes of neurologic character which were interpreted to be of vascular origin. At autopsy, vascular lesions like those being discussed in this paper, were present in the brain. No similar lesions were found in other organs. We are grateful to Dr. Moosy for showing these sections to us.

Attention may also be directed to the case reported by Zelling and von Meyerberg in *Schweizerische medizinische Wochenschrift* (72:825-826, 1942) of a 21-year-old man with neurologic abnormalities, "like those of multiple sclerosis." Histopathologic study of the brain showed multiple perivascular granulomas which included giant cells. A calcified primary tuberculous nodule in the lung is also described. The case was thought to be tuberculous in character, possibly Boeck's sarcoid, the latter being considered a form of tuberculosis. Although the data are incomplete, the case does resemble those reported here.

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