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THE NEUROLOGICAL MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

A Clinical-Pathological Study of 24 Cases and Review of the Literature

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I. Introduction

In the earliest clinical reports of systemic lupus erythematosus (SLE) neurologic abnormalities were described; yet in subsequent years this subject has not received the extensive clinical and pathological study given the renal, cardiac, cutaneous, or hematologic manifestations of the disease. In the original description of SLE in 1872, Kaposi (95) mentioned disturbed cerebral function associated with the disease, which took the form of recurrent delirium in 2 of his 11 patients. Osler (146–148), who was largely responsible for bringing the systemic nature of the disease to the attention of the medical profession, also described neurologic manifestations, namely recurrent hemiplegia and delirium, among the "visceral complications of erythema." The third classic contribution to the literature on SLE was the description of verrucous endocarditis by Libman and Sacks (115) in 1924; they reported convulsions, nuchal rigidity or paralysis in each of their four patients and postulated that neurological disease resulted from emboli arising from the endocardial lesions.

Until diagnosis was facilitated by the discovery of the L.E. phenomenon by Hargraves et al (82) in 1948, SLE was considered a rare disease. However, Dubois' (52, 54) studies at Los Angeles County Hospital since 1948 have shown that the diagnosis of SLE has been made more frequently than pernicious anemia, Hodgkin's disease, or leukemia; and, although previously neurological manifestations had been considered an unusual complication of a rare disease, his studies (54, 56, 57) have indicated that cerebral disease is one of the most frequent causes of death.

Thus, involvement of the nervous system in SLE is an important aspect of a not uncommon disease, but the neurological manifestations are protean and their pathological basis is still ill-defined. Seizures, psychosis, delirium, cranial nerve palsies, hemiplegia, myelitis, neuritis, and movement disorders have been included in the clinical descriptions of SLE. These disorders have generally been thought to result from intrinsic disease of cerebral blood vessels,

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but no distinctive lesions have been found. A large variety of encephalopathies, hemorrhagic and ischemic lesions, arteritis, phlebitis, and emboli have been described; and, not uncommonly, neuropathological studies have failed to demonstrate any abnormalities that might be correlated with the clinical signs.

The present study was undertaken in an attempt to define the neuropathological changes associated with SLE and to correlate these with the various clinical manifestations. A relatively unselected group of patients dying of SLE was studied in order to analyze the frequency, nature, and course of neurological manifestations; to review critically the neuropathological material; and to attempt a correlation of the clinical and pathological findings.

II. GENERAL CONSIDERATIONS

A. Method of Selection of Cases

Cases were included in this study 1) if a diagnosis of SLE was made clinically and confirmed at autopsy exclusive of neurological and neuropathological findings, and 2) if the clinical observation and completeness of autopsy were adequate to allow evaluation of neurological and neuropathological aspects. Records of all autopsies performed at the Massachusetts General Hospital during a 15-year period from 1945 to 1960 were reviewed; in 31 cases a pathological diagnosis of SLE had been made; the central nervous system (CNS) was examined in 25. One patient was observed only terminally and was excluded for lack of clinical data. The remaining 24 cases comprise this study. In each of these the clinical charts and autopsy protocols were reviewed, and neuropathological sections were reexamined in detail, irrespective of whether or not the patient had had neurological signs or symptoms. Additional sections were obtained and additional staining methods were employed when indicated.

B. General Clinical Findings

The 24 patients had all been admitted to the Massachusetts General Hospital from 1 to 10 times and followed for periods of 1 month to 10 years. Twelve were seen at least once by consultants from the Neurology Service. Twenty-two patients were female and 2 were male; ages at time of onset ranged from 15 to 46 years (mean 25.6 years, median 22.5 years); and duration of disease ranged from 3 months to 10 years (mean 3.0 years, median 2.0 years). The onset of SLE was dated from the first systemic symptom, since one patient had swelling and pain in one knee for 16 years and another had discoid lupus for 10 years before signs or symptoms of systemic disease. Initial manifestations other than fever, malaise, anorexia, and fatigue are shown in Table 1.

TABLE 1

*Initial Manifestation of SLE in 24 Patients**

	No. Patients
Arthralgias	15†
Rash	6
Lymphadenopathy	1
Parotid swelling	1
Pneumonia with hemoptysis	1

* Excluding fever, weight loss, malaise, and fatigue.

† One patient had a positive Hinton one year prior to arthralgias.

Clinical and laboratory findings are summarized in Table 2. Fever, some cutaneous change, albuminuria, and elevated erythrocyte sedimentation rates ultimately developed in all patients. The L.E. cell phenomenon was demonstrated in all patients seen after 1950. All patients except one developed arthropathy, but gross deformities of joints were rare. Anemia developed in all but one of the patients and leucopenia in all but two. Neurological symptoms or signs were next in frequency (75%); they were observed as often as gastrointestinal signs and symptoms and more often than serositis (including pleuritis and pericarditis) or the classic butterfly rash (71% each).

As Harvey et al (84) have stressed, an exact cause of death is difficult to ascertain even pathologically because of the diffuseness of lesions. Infection and renal or cardiac failure were most frequently considered to be the primary cause of death.

C. General Pathological Findings

The most significant pathological features are summarized in Table 3. In two cases there were unusual findings that have been the subject of previous case reports; one of the patients, in whom parotid swelling was the presenting symptom, had Mikulicz's syndrome (31, 135), and the other had massive bilateral

TABLE 2

Clinical Findings in 24 Patients with SLE

	No. Patients	Percent
General		
Fever	24	100
Weight loss	21	88
Cutaneous		
Butterfly rash	17	71
Hair loss	12	50
Raynaud's phenomenon	2	8
Ophthalmological		
"Cytoid bodies"	2	8
Hemorrhages and exudates	5	21
Arthralgias and arthritis	23	96
Lymphadenopathy	14	58
Serositis (pleuritis and/or pericarditis)	17	71
Hepatomegaly	15	62
Splenomegaly	9	38
Gastrointestinal	18	75
Bleeding	4	17
Severe abdominal cramps	4	17
Dysphagia	2	8
Renal		
Albuminuria	24	100
Uremia	12	50
Nephrotic syndrome	5	21
Parotid swelling	2	8
Severe epistaxis	3	13
Hematological		
Anemia (below 11 g)	23	96
Leucopenia (below 4500)	21	88
Elevated erythrocyte sedimentation rate (over 30)	24	100
False positive serological test for syphilis	3	13
Positive L.E. phenomenon	16	100*
Neurologic and psychiatric	18	75

* Eight patients died prior 1950 and were not examined for L.E. cells.

perirenal hematomas (32). No single characteristic pathological lesion occurred in all cases, but in each case a combination of lesions allowed an unequivocal diagnosis of SLE.

D. Summary

These general findings are summarized to establish these cases as representative of the clinical and pathological syndrome of SLE. The age, sex, mode of onset, and clinical findings are similar to those reported in several larger clinical series (7, 16, 29, 57, 84, 88, 94, 107). The nature and frequency of pathological findings are also similar to those previously described (63, 94, 101, 102).

III. REVIEW OF NEUROLOGICAL MANIFESTATIONS WITH ILLUSTRATIVE CASES

A. Frequency and Course

Neurological and psychiatric signs or symptoms were recorded in 18 of the 24 patients (75%) in this study (Table 2). This frequency is higher than the 20 to 65 percent incidence of neurologic involvement reported by others (7, 16, 18, 33, 57, 84, 88, 107, 119, 125, 144), although Gold and Yahr (74) reported neurological disease in 13 of 14 children with SLE. The fact that patients in the present series were followed until death probably accounts for this high frequency since neurological involvement occurred only during the last 6 weeks of life in 9 of the 18 patients. A further factor influencing this frequency was the exclusion of six cases because of the inability to examine the CNS at autopsy; indeed, only one of these six patients had neurological signs during life. However, frequency of neurologic manifestations would be 62 percent even if all cases had been included.

Seizures and mental disorders are generally regarded as the common neurological abnormalities associated with SLE, but any part of the nervous system may show evidence of disease (Table 4). Furthermore, neurological disease with SLE is varied not only in its clinical signs but in its clinical course. The development

TABLE 3

General Pathological Findings in 24 Patients with SLE

	No. Patients	Percent
Verrucous endocarditis (wart-like)	8	33
Myocardial lesions	13	54
Pericardial lesions	17	71
"Wire loop" lesions in kidneys	14	58
"Onion skin" lesions in spleen	11	46
Focal lymph node necrosis	7	29
Vasculitis*	7	29

* Excluding nervous system; in three cases "vasculitis" was limited to perivascular infiltrates in skin and/or muscle.

of neurological signs has been regarded as ominous, since they are commonly observed during an acute phase of disease or before death (84, 173). In one study, Dubois et al (56) concluded that CNS involvement was the commonest cause of death, and in his more recent series (57) death was attributed to CNS disease in 18 percent of 135 cases, ranking second only to uremia. Death was attributable primarily to CNS disease in 6 of the 24 patients in this study; 4 died of intracerebral hemorrhage and 2 in status epilepticus. Despite their potentially fatal nature the appearance of neurological signs and symptoms does not necessarily imply a dire prognosis. The neurological signs can be minor and transient and can even precede the clinical involvement of other systems; seizures (29, 38, 74, 79, 81, 107, 133, 166, 175), psychosis (27, 58, 107, 195), hemiplegia (29, 147, 161, 188), encephalopathy (206), neuropathy (74, 88), myelitis (77, 188), chorea (25, 151), diplopia (83, 188), and paresthesias (83, 98, 188) have all been reported as initial signs and symptoms of SLE. In the present study none of the patients presented with neurological manifestations, but 7 of the 18 patients with neurological disorders had these signs or symptoms one year or more before death.

The varied nature of CNS involvement in both its major and minor aspects is exemplified by the following patient who had numerous transient neurological signs over a 9-year period and died in status epilepticus.

Case 1

This 27-year-old woman was seen intermittently at the hospital from age 3 because of recurrent bilateral otitis media with resultant bilateral hearing loss and left facial palsy. At age 17 she developed migratory arthralgias and anemia followed by recurrent fever and Raynaud's phenomenon. At age 18 years she developed clinical arthritis and was found to have anisocoria (left pupil larger than the right), hyperreflexia, and bilateral ankle clonus. L.E. cell preparations were negative. At age 20 she was admitted with another episode of otitis complicated by diplopia and vertigo, and previous neurological signs were no longer present. However, she had ataxia of the left arm and leg, left-sided hyperreflexia, and a left extensor plantar response. Opticokinetic nystagmus was diminished with the targets moving to her right.

TABLE 4

Neurologic Manifestations in 24 Patients with S

	No. Patients	Perce
Seizures	13*	5
Cranial nerve disorders	10	4
Hemiparesis	3	1
Paraparesis	1	4
Peripheral neuropathy	2	8
Mental disorders	8	3

* One case had idiopathic epilepsy.

Electroencephalogram and spinal fluid examination were normal. Albuminuria was present f the first time. At age 23 a red, burning butter rash developed. The facial paralysis, left hype reflexia, and recurrence of anisocoria were t only abnormal neurological findings. One L cell was found on numerous preparations. At a 26 she was admitted because of microscop hematuria, but renal function studies and bloo pressure were normal; the L.E. phenomeno was strongly positive for the first time. All a normal neurological findings had disappeared ex cept the facial paralysis. Five months later sh complained of numbness of the left side a was found to have hypalgesia of the left trun and leg with sparing of the arm and face. Tw months after this she was admitted for the 10t and final time with acute right flank pain. Bloo pressure increased from 130/80 to 190/100, t hematocrit fell, and a right upper quadrant mas developed; a right nephrectomy was performe with evacuation of a massive subcapsular an perinephric hematoma. The blood pressure re turned to normal after the operation, and th blood urea nitrogen was 26 mg/100 ml. She com plained of generalized weakness and was foun to have vertical and horizontal nystagmus slurred speech, weakness of the right arm, hyp esthesia over the left 6th to 8th cervica dermatomes, bilateral hyperreflexia with a bris jaw jerk, absent abdominal reflexes, and bilatera extensor plantar reflexes. Spinal fluid was agai normal. Strength was improving when on the 21s postoperative day left flank pain with a mass an increase in blood urea nitrogen to 120 mg/10 ml. and a rise in blood pressure to 160/100 de veloped. Corticosteroids were given for the firs time. In one week the blood urea nitrogen re turned to normal. She was alert but had marked emotional lability; other neurological findings were unchanged. The blood pressure remained moderately elevated. Suddenly 31 days postoperatively and 19 days after steroids were begun, she

developed generalized seizures which could not be controlled with anticonvulsants. She became apneic requiring a respirator, and blood pressure fell despite vasopressors. Spinal fluid examination during convulsions showed a pressure of 230 mm, protein of 46 mg/100 ml, and no cells; seizures continued until death a few hours later.

General postmortem examination showed fibrinoid degeneration of vessels consistent with the diagnosis of SLE. Perinephric hematomas and arteritis were found in both the surgically removed and remaining kidney. General findings are described in detail elsewhere (32). The brain weighed 1300 g. On coronal section there was an old softened infarct at the left caudatoputaminal junction extending from the level of the anterior commissure to that of the genu of the corpus callosum. Throughout the cerebral hemispheres there were small hemorrhagic lesions (less than 2 mm) mainly in subcortical white matter.

Microscopic examination showed numerous microinfarcts especially in the cerebral cortex and brainstem. One old infarct extended obliquely across the pyramidal tract in the medulla, and there was secondary degeneration of the corticospinal tract in the spinal cord. The large blood vessels appeared normal, but the small arterioles and capillaries were unusually prominent particularly in the cerebral cortex. Some small vessels were surrounded by fibrin and others by an increase in microglia. The walls of a few of these vessels were necrotic, and occasionally there was occlusion of the lumen with fibrin. Small extravasations of red blood cells into the parenchyma were associated with these changes. No inflammatory cells within the vessel walls or in the perivascular spaces were found.

B. Specific Neurological Abnormalities

1. Seizures. Seizures are commonly observed in the course of SLE, occurring both early and late in the disease. They can be transient or recurrent and take a variety of clinical forms. In most instances seizures have been regarded as a primary manifestation of SLE, although seizures may also occur secondary to uremia, hypertension, or steroid therapy.

The reported frequency of seizures ranges from 57 percent (74) to 7 percent (94). Russell et al (175) reviewed 114 cases of SLE in the literature before 1950 and determined a frequency of 15 percent. Combining the data of several large subsequent series (7, 16, 18, 33, 41, 57, 74, 75, 84, 86, 88, 94, 144, 187, 193, 195), which include a total of 1540 patients, seizures are found reported in 214 patients, giving a similar frequency of 14 percent. Since patients were not all followed until death in these clinical series, this figure does not reflect a total frequency.

The 54 percent incidence of seizures in the present series is not surprising, however, since seizures often occur in the terminal phases of SLE. Terminal convulsions occurred in 11 of 16 patients dying of SLE in a series reported by Dubois et al (56); in the review of Russell et al (175) 15 of the 22 reported convulsive disorders developed terminally. Convulsions appearing for the first time during the last days of life have frequently been noted by others (10, 11, 18, 49, 66, 109, 114, 115, 121, 127, 144, 151, 158, 175, 184, 199, 207, 213, 221). Of 75 patients dying of SLE O'Connor and Musher (144) reported seizures in 30 percent.

Nevertheless, the development of seizures does not necessarily herald death. Montgomery and McCreight (133) emphasized the occasional occurrence of convulsions early in the course of disease, and Russell et al (175) described two patients with seizures preceding other signs of SLE by two and 16 years. Subsequently seizures have been reported one to 20 years before other signs or symptoms (66, 79, 81, 166).

Seizures may occur during an exacerbation of disease and not recur subsequently, or a recurrent convulsive disorder may develop. Solitary seizures or a group of seizures occurring early in the course of illness with no recurrence have been described (4, 65, 90a, 142, 198). Conversely, recurrent seizure disorders extending over a year or more may develop (72, 84, 158, 160, 175, 221). Harvey et al (84) and Poch (158) have both reported patients with post-traumatic epilepsy in whom the seizure disorder was accentuated shortly before or coincident with the onset of SLE. The majority of convulsions described have been generalized motor seizures, but focal or Jacksonian seizures (21, 38, 59, 93, 103, 126, 149, 158, 198, 201, 203, 212), psychomotor seizures (158), and absence attacks (164) have been reported. Neuropathological studies of patients with seizures have, in the majority of cases, shown one or more areas of cortical infarction (4, 72, 74, 114, 121, 136, 137, 159, 198). Terminal Jacksonian seizures, however, have been related to intracerebral hemorrhage (203) and subarachnoid hemorrhage (212). Only one case

has been studied pathologically in which seizures antedated other manifestations of SLE, and in this case it is significant that no neuropathologic abnormalities were found (81). The coincidental association of epilepsy and SLE must be considered in cases such as this where the seizure disorder antedated the onset of SLE by 11 years.

The relationship of SLE to a pre-existing convulsive disorder has been further obscured by the recent observations of lupus-like syndromes induced by anticonvulsants. In 1953 Miescher and Delacretaz (128) attributed a case of SLE to anticonvulsant medication, and this association of hydantoins with SLE was supported by reports in 1957 of eight cases by Ruppli and Vossen (174) and two cases by Lindqvist (117). Trimethadione and other anticonvulsants have now been implicated by subsequent reports (3, 17, 91, 108, 153, 179, 217). Clinically the syndrome of SLE is typical including a positive L.E. cell phenomenon, and in an autopsied case typical lupus nephritis and vascular lesions were found (17). In these cases a reversal of clinical findings and the L.E. phenomenon has usually occurred subsequent to the withdrawal of the drug (3, 17, 91, 108, 162, 174) and Rallison et al, (162) reported a case in which a renal biopsy showed "wire loop" lesions but a subsequent biopsy 19 months later (26 months after stopping diphenylhydantoin) showed no "wire loops." In some instances, however, apparent drug induced SLE syndrome may persist or progress even after withdrawal of anticonvulsants (90, 91, 108). Whether such cases represent drug-induced disease, the unmasking of SLE by medication, or simply a convulsive state due to SLE in which the anticonvulsant played no causitive role still remain a matter of speculation.

Seizures occurred in 13 of the 24 patients in this series. One patient (Case 3) had a convulsive disorder since infancy and was considered to have idiopathic epilepsy; seizures did not become more frequent or severe with the development of SLE, despite the appearance of other neurological manifestations and finding of microinfarcts pathologically. The remaining 12 patients all had seizures after the development of other systemic symptoms, and 9 had neurological or psychiatric abnormalities in addition to the convulsive disorder. Two patients (Cases 6 and 16) had a single episode of generalized convulsions four and one years before death respectively, with no recurrence even though anticonvulsants were not given. Five patients (Cases 2, 7, 8, 11, and 14) had recurrent seizures of six years to five weeks in duration, and five patients (Cases 1, 10, 12, 17, and 18) had seizures only terminally. In Cases 17 and 18 terminal seizures were associated respectively with uremia and sepsis, and clinically seizures were regarded as secondary to these complications. Three patients (Cases 2, 14, and 16) had Jacksonian seizures.

The potential severity of convulsive states in SLE was seen in three patients who developed status epilepticus. In Case 11 this was secondary to a large intracerebral hemorrhage and in Cases 1 and 10, where death resulted from status epilepticus, there were multiple small ischemic and hemorrhagic lesions in the cerebral cortex. In most other cases with seizure disorders multiple microinfarcts in the cerebral cortex were found.

The following case provides an example of recurrent focal seizures which for six years were the most prominent symptom of SLE.

Case 2

This 49-year-old woman developed a rash diagnosed as erythema multiforme at age 43. A mild leucopenia and anemia were found, and shortly thereafter hepatosplenomegaly and arthritis developed. Five months later she had a generalized convulsion. She had pleuritis and pericarditis at that time, and the L.E. phenomenon was demonstrated. The blood pressure was normal and no evidence of renal disease was found. During the next six years she remained reasonably well except for recurrent major and minor seizures. Almost continually she experienced a flickering of light in her left visual field, which she compared to the opening and closing of a venetian blind; she also complained of bumping into objects on her left. The convulsions took a variety of forms, but they usually began with pounding bi-temporal headaches, nausea, and diaphoresis; this was followed by burning and tingling in the left hand and then jerking of the left arm and left side of the face without loss of consciousness. Occasionally these prodromata were followed by a generalized motor seizure. Repeated neurological examinations disclosed no abnormality of visual fields; there was a left supranuclear facial weakness and a slight decrease in motor strength in the left extremities. Tendon reflexes were symmetrical, but the

left plantar response, although not clearly extensor, was abnormal. Electroencephalogram showed diffuse low voltage with non-focal paroxysms of high voltage delta activity. Seizures were reduced in frequency but never completely controlled by diphenylhydantoin. On the day of her final admission she awoke with a severe left frontal headache and weakness of the left limbs; shortly thereafter she had a generalized convulsion. On admission the blood pressure was 190/90; there was a left flaccid hemiplegia and hemianesthesia. A lumbar puncture revealed bloody fluid with a pressure of 240 mm. She became comatose and died 36 hours after admission.

General postmortem examination showed verrucous endocarditis, lupus nephropathy, adhesive pericarditis, onion skin lesions in the spleen, and fibrinoid degeneration in vessels. The brain weighed 1230 g; there was herniation of the right temporal lobe and compression of the midbrain. Within the right cerebral hemisphere there was 4 x 4 cm recent hemorrhage which extended from the Sylvian fissure posteriorly to the splenium of the corpus callosum. In addition, in the subcortical white matter of the region of the right superior parietal-occipital junction there was a slit-like cavity with smooth yellow walls extending 3.5 cm in length.

Microscopic examination showed that the walls of the cavity in the right parietal-occipital region contained numerous hemosiderin-laden macrophages-findings typical of an old hemorrhage. The perivascular spaces of many small blood vessels in the tegmental portion of brainstem were infiltrated with lymphocytes with a few lymphocytes within vessel walls themselves. Small arterioles and capillaries appeared to be abnormally prominent throughout the cerebral cortex and brainstem, and microglia were increased around these vessels.

2. Cranial Nerve Disorders. Many abnormalities of cranial nerve function have been described with SLE; however, these abnormalities may be brought about in several ways. They may be the result of lesions in corticobulbar tracts at a cerebral level, of intramedullary lesions within the brainstem, of lesions within the peripheral cranial nerves themselves, or of a disorder at the myoneural junction resembling myasthenia gravis. All of these mechanisms have been reported to occur in SLE.

Defects of vision are frequent but often are related to retinal changes; these changes have been well characterized clinically and pathologically (42, 68, 89, 123, 209). Blindness (49, 136, 175, 184) and homonymous hemianopic defects (18, 49, 190, 213, 221) presumably due to cerebral lesions have been reported. Papilledema has been seen (16, 33, 66, 74, 84, 96, 107, 123, 142) with normal spinal fluid pressure (58, 123, 184) and with increased pressure (66, 90a, 177), and optic atrophy has also been reported (85, 86, 142, 183, 185, 177).

The most frequent cranial nerve abnormalities associated with SLE are related to extraocular movements and pupillary abnormalities (119). It is in these instances that the anatomic level of the lesion is often in doubt. Myasthenia gravis may be suggested by abnormalities of extraocular movements, and in 1954 Harvey et al (84) described a patient with ptosis and diplopia in whom a diagnosis of myasthenia gravis was made a year before the rash and other stigmata of SLE appeared and in whom the myasthenia-like symptoms never returned (35). Subsequently, a number of cases with an apparent myasthenic syndrome associated with SLE were reported (45, 65, 171). Harvey and Johns (83) reviewing cases prior to 1962 felt that "while the diagnosis of lupus appears definite the manifestations attributable to myasthenia gravis are atypical and respond poorly to anticholinesterase therapy". However, the literature now contains several reports of anticholinesterase-responsive myasthenia gravis developing before (48, 67, 154) and after (65, 99, 120, 215, 220) signs of SLE. This frequency of association has given rise to speculation on the immunologic nature of both disorders (67, 154, 191, 222).

In most instances, however, abnormalities of extraocular movement are associated with other cranial nerve paresis (10, 41, 104, 127, 142, 160, 202) or the involvement of ascending or descending pathways (34, 104, 188, 202) clearly indicating that they result from lesions within the brainstem. Abducens nerve palsies with a severe motor neuropathy (97) and secondary to increased intracranial pressure (130, 177) have also been described.

Tinnitus and vertigo have been listed as common neurological manifestations of SLE (119), but the possible relationship of these symptoms to salicylate intoxication makes their evaluation difficult. In several cases vertigo has been associated with other brainstem or long tract signs, and in these cases it almost cer-

tainly resulted from a lesion within the brainstem (90a, 104, 105, 213). Larson (107) has listed Meniere's syndrome as a neurological complication of SLE in two patients, but the nature of this disorder was not further defined.

Neuropathological studies of cases with cranial nerve disorders have uniformly shown vascular lesions within the brainstem. Bailey et al (10) reported diplopia, nystagmus, left facial hypesthesia, and intention tremors in a patient and correlated these findings with areas of infarction in the medial longitudinal fasciculus, gasserian ganglion, and restiform body. Morsier (136, 137) has described one patient with a right third nerve palsy, inability to look upward, left facial weakness, dysarthria, left hemiparesis and bilateral cortico-spinal tract signs; and another with an episode of blindness followed by coma, third nerve palsy, left hemiparesis with subsequent seizures, anarthria, and loss of sphincter control. At autopsy multiple areas of infarction were found in both cases. Cluxton and Krause (36) described a patient with transient diplopia and vertigo who had a small perivascular hemorrhage in the pons. Contador Caballero et al (39) described bilateral third nerve palsies, a right infranuclear facial weakness, right hearing loss, and paresis of palate with a hemorrhagic infarct in the midbrain and fibrinoid degeneration of vessels in the medulla. Friedberg et al (64) reported "transient cranial nerve palsies" during life but did not correlate them with the diffuse encephalomalacia found at autopsy. There have been no documented cases of cranial nerve palsies resulting from lesions within the nerve as seen in periarteritis nodosa and diabetes mellitis (51, 131).

Ten patients in this study had abnormalities of cranial nerve function; none had signs or symptoms suggesting myasthenia gravis, but in two cases signs probably resulted from cerebral rather than brainstem lesions. In Case 2 there was a longstanding left supranuclear facial paresis secondary to a right parietal-occipital hemorrhage, and in Case 11 papilledema and ophthalmoplegia resulted terminally from a large intracerebral hemorrhage. Nevertheless, at autopsy lesions within brainstem were found in both cases. Of the remaining patients three developed cranial nerve abnormalities terminally. One patient (Case 9), who had a right intracerebral hemorrhage with divergent gaze and a dilated fixed right pupil, had previously developed sudden bilateral nerve deafness which might be accounted for by numerous microinfarcts found within the brainstem. Another (Case 10) developed bilateral ophthalmoplegia five days before death in status epilepticus; and many microinfarcts and small hemorrhages were found in brainstem as well as cerebral cortex. A right supranuclear facial palsy developed secondary to a fatal pontine hemorrhage in the third patient (Case 13). Case 12 has previously been reported by Cogan et al (37). This patient developed a right internuclear ophthalmoplegia 12 days before death which correlated with a small infarct in the right medial longitudinal fasciculus found at autopsy.

In four patients the cranial nerve disorders were transient and occurred early in disease. In Case 1 transient anisocoria nine and four years before death and nystagmus and dysarthria during the last month of life were found; in Case 6 a transient left sixth nerve palsy developed four years before death; and in Case 7 transient diplopia due to loss of convergence occurred one year before death. Specific pathological lesions could not be correlated with the transient signs in these 3 patients, but old microinfarcts were found in each case. In contrast, the following patient had a transient third nerve palsy six years before death with clinical features suggesting a lesion within the peripheral nerve.

Case 5

This 23-year-old woman had had a convulsive disorder dating from infancy, but she was otherwise well until age 15, when she developed fever and arthritis. Seven months after the onset of the arthritis she developed severe left upper quadrant pain and was found to have massive splenomegaly and a white blood count of 400 mm³. Platelets were not decreased. She awoke one morning with headache and diplopia. Examination revealed there was limitation of movement of the left eye in all directions except lateral gaze. There was no ptosis; the pupils were equal in size and reacted to light. Blood pressure was normal, and there were no other neurological abnormalities. The diplopia cleared completely in ten days. During the next seven years she developed renal and cardiac disease and L.E. cells were demonstrated, but no further neurological signs or symptoms developed. She was intermit-

gradly treated with steroids with no increase in the frequency of her seizures. She died in renal failure.

Postmortem examination showed thrombosis of the right atrium, pulmonary congestion with focal hemorrhages, pericardial effusion and passive congestion of the liver with central necrosis. Wire loop lesions of SLE were present in the kidneys. The brain weighed 1080 g and was grossly normal. Microscopic examination showed a general prominence of vessels many of which were surrounded by microglia. This was particularly prominent in the posterior columns of the spinal cord. No infarcts, hemorrhages, vasculitis or perivascular inflammation was found. The peripheral third cranial nerve was unfortunately not obtained for examination.

3. Hemiparesis. Hemiparesis is an infrequent complication of SLE; in large clinical series Dubois (52) reported a frequency of 5 percent, Clark and Bailey (33) 4 percent, Harvey et al (84) 2 percent, and Armas-Cruz et al (7) found no cases; Cook et al (40) mentioned two cases of hemiplegia in a series of 37 children with SLE. In 1900 Osler (147) reported the first and most unusual case of hemiparesis associated with SLE; he described a young physician who had five or six transient episodes of hemiparesis with aphasia occurring over a 14-year period before the development of rash and nephropathy. The relation of the motor disorder to SLE is uncertain in this patient as in a patient subsequently reported by Pryse-Phillips and Yorkston (161) who developed a sudden hemiparesis eight years before the signs of SLE and a patient reported by Rudusky (172) who had transient hemiparesis and aphasia 32 years preceding signs of SLE. Siekert and Clark (188) reported hemiparesis antedating other manifestations of SLE by six months, and Silverstein (190) reported five patients who first sought medical care with major cerebrovascular accidents, although in retrospect all proved to have had mild antecedent symptoms of SLE. In contrast, a number of reports have described terminal hemiplegia (6, 52, 66, 81, 127, 132, 152, 196, 213), but of the over 50 reported cases of hemiparesis the majority occurred at some intermediate stage of disease (8, 9, 13, 20, 23, 38, 49, 65, 66, 90a, 116, 132, 136, 137, 141, 158, 168, 180, 213). The recurrence of hemiparesis in Osler's patient remains unique, although Sedgewick and Von Hagen (180) described a young woman who developed a mild left hemiparesis followed four months later by aphasia and mild right hemiparesis; in this patient both deficits resolved, and she remained free of neurologic disease for the next eight years.

Both the recurrence of hemiparesis and the sudden onset of major motor deficits associated with aphasia, hemianopia, or sensory loss suggest the occlusion of major cerebral vessels. Cerebral arteriography has been performed on several patients developing hemiplegia, and the apparent occlusion of major arteries has been described in six patients (20, 49, 190). In contrast, one patient was reported with sudden right hemiplegia, aphasia, and mild sensory loss who had a normal cerebral arteriogram (190). Patients with hemiparesis reported by Meagher et al (26) and Fulton and Dyken (66) had arteriograms which erroneously suggested tumors; in both cases this led to surgical exploration with the finding of infarcted brain tissue.

Despite these radiological studies occlusions of large or medium-sized arteries have not been a common finding pathologically. One of the patients with arteriographic evidence of left middle and anterior cerebral artery occlusions came to autopsy three years later, and a large area of infarction in the left cerebral hemisphere was found; description of the left middle cerebral vessel was limited to "healed arteritis" (190). Twelve other pathological studies on patients with hemiparesis were found in the literature, and only one described occlusion of large arteries. This patient reported by Honda (90a) had thrombotic occlusion of the left internal carotid, right vertebral, and basilar arteries. Two cases reported by Morsier (136, 137) with hemiparesis three and six years antemortem had multiple small lesions with occlusions of small arteries or arterioles. Two patients reported by Mintz and Fraga (132) had areas of infarction associated with inflammatory reactions but no vascular occlusions. A case reported by Lief and Silverman (116) with hemiparesis and aphasia four years before death had a large fronto-temporal infarct, but no vascular lesions were noted. Fulton and Dyken (66) in a patient dying two months after the onset of hemiplegia, found a large hemorrhagic frontal infarction with recanalized pial veins over the infarcted area and hyalinized arterioles in the subarachnoid space and cortex. Naso-

nova and Konchakova (141) found an old intracerebral hemorrhage to account for a preceding hemiplegia. In cases with terminal hemiparesis Andreucci (6) reported a large area of hemorrhagic infarction; Tumulty and Harvey (203) and Weingarten and Braunsteiner (213) have found large intracerebral hemorrhages; and Hanrahan (81) found a subarachnoid hemorrhage without an apparent source of bleeding.

In the present series three patients had hemiparesis. In addition, one patient (Case 1) had a transient left-sided hyperreflexia and extensor plantar reflex without demonstrable weakness. The three patients with definite hemiparesis all had focal seizures which began on the hemiparetic side. In Case 2 an old intracerebral hemorrhage resulted in mild hemiparesis of six years' duration, and a second large intracerebral hemorrhage led to total hemiplegia and death. Similarly, in Case 11 hemiplegia and death resulted from a large intracerebral hemorrhage. The third patient (Case 14) had a generalized seizure six weeks before death, and thereafter, had a mild right hemiparesis; she also had recurrent Jacksonian seizures beginning in the right abdominal muscles and spreading to the right limbs before becoming generalized. At autopsy a small area of cortical softening was present in the left frontal lobe; and microscopically many microinfarcts were found in the cerebral cortex and the brainstem. Recent and old microhemorrhages were also found in the pons and cerebellum.

4. *Paraparesis.* Although disease of cerebrum and brainstem is common in SLE, clinically significant involvement of the spinal cord is rare. Only 14 patients with definite signs of spinal cord disease were found reported in the literature. Siekert and Clark (188) reported myelitis with partial recovery which preceded other signs of SLE by three years, and Granger (77) described a patient who presented with transverse myelitis but who had laboratory evidence of nephropathy, abnormal serum proteins, and positive L.E. cell preparations. Four patients with SLE and paraparesis have been reported who had subsequent recovery or improvement (7, 13, 139), and brief mention is made of two additional patients with spastic paraparesis in other reports (141, 158).

Six patients with paraplegia occurring late in the course of disease have been reported with neuropathological studies. In 1939 Fisher and Gilmour (61) reported a 33-year-old woman with classic SLE who suddenly developed flaccid paraplegia and loss of touch sensation below the iliac crests. Position and vibratory sensation were preserved. The sensory loss ascended to the second thoracic segment over the next four days until death. Postmortem examination of the spinal cord showed thrombosed veins with lymphocytes in the adventitia and a single thrombosed small artery with fibrinoid degeneration and lymphocytic infiltration of the vessel wall. Widespread perivascular necrosis was also found. The authors ascribed these lesions to sulfanilamide therapy and, therefore, this case has been overlooked in subsequent reports of paraparesis related to SLE. Piper (157) described a similar patient with ascending weakness, paresthesias, and sensory loss and urinary retention who had similar pathologic findings in spinal cord and brain. Orthner and Rossner (145) reported a young man with transverse paralysis at the 7th thoracic segment whose spinal cord showed microhemorrhages, thickened capillaries with fibrinoid changes, and perivascular inflammatory reactions from the mid-cervical to the mid-thoracic cord. Dubois (52) briefly mentioned a patient with paraplegia who had "arteritis in spinal cord." An entirely different cause of sudden terminal paraplegia has been reported in two other patients (35, 212), who proved to have spinal subdural hemorrhage with cord compression. Although no vascular pathology was evident in the cord in either case both had arteritis resembling polyarteritis nodosa elsewhere, in the viscera in one case (212) and in the brain in the other (35).

In the present series several patients had signs of bilateral lesions involving the corticospinal tract; but only the following patient had paraplegia clearly related to disease of the spinal cord.

Case 4

This 43-year-old woman died of SLE after an 18-month illness in which paraparesis during the last 12 months and a severe psychosis during the last 3 months were the major disabilities. Her illness began with the development of a butterfly rash unaccompanied by systemic symptoms. Laboratory studies showed a leucopenia, and a skin biopsy was consistent with SLE, but L.E.

preparations at the time were negative. Six months later she developed progressive stiffness and numbness of the legs with urinary frequency and incontinence. Cortisone was started, and four days later she had a transient psychotic episode with paranoid ideas and auditory and olfactory hallucinations. Her leg weakness increased gradually over the next four months, and she was then readmitted with urinary retention and inability to walk. She was afebrile with a blood pressure of 100/70. A butterfly rash, mild hepatosplenomegaly, minimal effusions of both knees, albuminuria and positive L.E. phenomenon were present; the non-protein nitrogen remained normal over the subsequent eight months of hospitalization. She was oriented but showed poor retentive memory, impairment of calculation, and a paucity of general information. Insight was poor and her affect was inappropriate and euphoric; no delusions or hallucinations were detected. Examination of the cranial nerves and upper extremities showed no abnormalities. The lower abdominal and back muscles were weak, and the legs showed total flaccid paralysis. Abdominal reflexes were absent, tendon reflexes in the legs were brisk, and plantar reflexes were extensor. Pain and temperature sensation were reduced below the umbilicus and absent over the sacral dermatomes; touch sensation was only mildly impaired and position and vibratory sensation were intact. The anal sphincter was atonic, and a cystometrogram showed a neurogenic bladder. A lumbar puncture disclosed normal pressure and dynamics; three red blood cells and seven lymphocytes/mm³ of fluid, and a protein of 40 mg/100 ml. A myelogram of the lumbar, thoracic, and cervical regions was entirely normal.

During the next three weeks she was maintained on the dosage of cortisone begun prior to admission (100 mg/day); she had occasional outbursts of inappropriate singing and the level of sensory deficit rose to the costal margin despite apparent improvement of muscle strength. Over the subsequent two months cortisone was gradually reduced to 50 mg/day; strength continued to improve, and she became able to walk a few steps with assistance; the plantar reflexes became flexor. Then over a 2-day period she developed fever, increased rash, and increasing weakness of her legs. Disorientation developed followed by a mute state in which she followed simple commands only with difficulty. No movement of the legs could be found, and tendon reflexes in the arms became asymmetrical, being more active on the left; grasp reflexes were present bilaterally. A repeat lumbar puncture showed a pressure of 180 mm, no cells, and a protein of 102 mg/100 ml. Cortisone was increased to 150 mg/day, and fever and rash promptly abated; she became alert and talkative. The legs were now spastic but with weak movements at all joints; unsustained clonus was present at the knees and ankles, and the plantar reflexes were again extensor. Pain and temperature sensation were reduced below the clavicles, and vibratory sensation was mildly impaired at the ankles and toes.

For one month her status remained unchanged, and a slow reduction of cortisone dosage was again attempted. In three weeks her dosage was reduced to 100 mg/day with no change in her neurologic deficit, but she became hyperactive and euphoric with nonsense rhyming and punning. Over the next week she began having visual and auditory hallucinations and became intensely paranoid, threatening and attacking ward personnel. Her constant speech was rhythmic and scanning in iambic meter, described as "reminiscent of James Joyce". An electroencephalogram and repeat spinal fluid examination were normal. Over the next three months cortisone was increased to 300 mg/day and reduced again to 100 mg with no apparent effect on her psychosis. Her behavior required confinement on a disturbed psychiatric ward, and her paraparesis confined her to bed. Other manifestations of SLE were quiescent until her sudden death three months after the onset of the psychosis and one year after the onset of paraparesis.

Postmortem examination disclosed pulmonary infarcts with multiple fresh pulmonary emboli. There were onion skin lesions in the spleen but no cardiac or renal lesions. The brain weighed 1150 g and showed an old infarct 0.5 cm in length in the genu of the left internal capsule at the caudate-putaminal junction. The spinal cord showed irregular discoloration from the mid-thoracic level rostrally.

Microscopic examination of the brain showed multiple microinfarcts in the cortex and basal ganglia. The small arterioles and capillaries of the brain had prominent walls with apparent thickening of the endothelium, but the larger vessels were entirely normal. No occluded vessels were found. The spinal cord showed a remarkable subacute degeneration of the white matter from the cervical to the sacral segments. At the cervical, thoracic, and lumbar levels the lesion involved the entire circumference of the cord being most severe peripherally and extending into the posterior, lateral, and anterior columns (Fig. 1). At the sacral levels there was only slight involvement of the posterior columns, no abnormalities in anterior columns, and wedge shape lesions

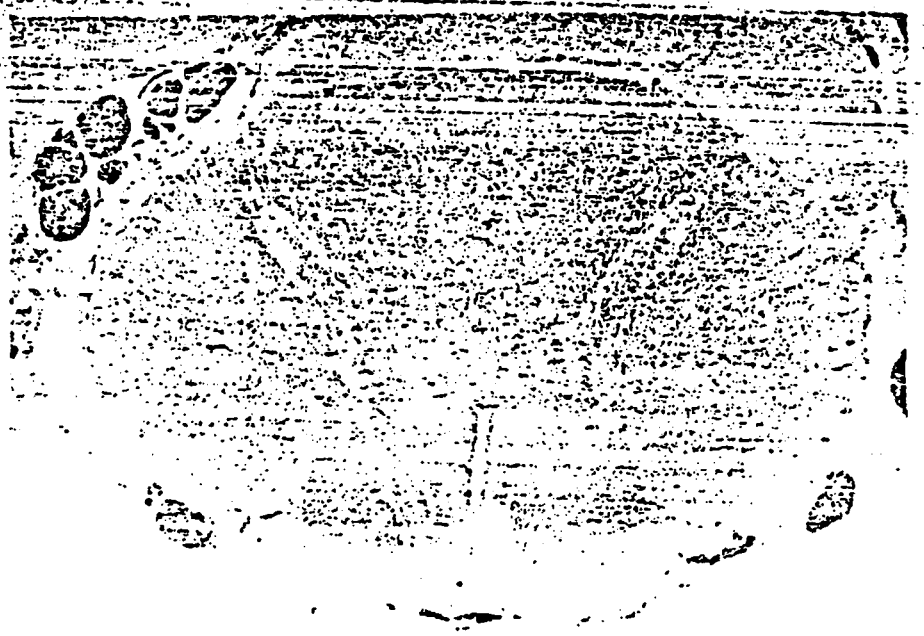

FIG. 1. Section of thoracic spinal cord from Case 4 showing myelin loss and vacuolar changes in white matter. Loyez stain, × 14.

in the corticospinal tracts consistent with secondary degeneration. The margins of the lesions bordering upon the normal white matter were not sharply demarcated; along these borders there were many vacuoles of varying size many of which, under high magnification, appeared to be swollen myelin sheaths. Fat stains showed large amounts of free fat in macrophages throughout the areas of involvement. Myelin and axis-cylinder stains showed that both myelin and axis cylinders were disrupted. No abnormalities were found in anterior or posterior roots or in the grey matter at any level. The large anterior and posterior vessels of the cord appeared normal. There was some thickening of the adventitia of small arteries and veins in the area of degeneration, but no occluded vessels were seen. In one level of cervical cord, there was a small focus of old subpial infarction.

5. Peripheral Neuropathy. Peripheral nerve disorders are seen less frequently than CNS disorders in SLE. An accurate incidence is difficult to determine from published series; several large reviews report no peripheral neuropathies (41, 75, 79, 94) or mention single cases (74, 84, 107), whereas others site incidences of 3 to 18 percent (7, 16, 18, 33, 55, 88). Poch (158) reported distal wasting, areflexia, or sensory deficits suggesting neuropathies in 10 of 20 patients.

The pattern of the neuropathy is variable. Some patients have had symmetrical distal motor and sensory loss similar to that seen in nutritional polyneuritis (5, 10, 80, 90a, 103, 186, 204, 213); others have been reported with predominant or exclusive motor loss and elevated spinal fluid protein resulting in a Guillain-Barre syndrome (10, 18, 69, 76, 87, 97, 113, 177, 189). The evolution in these cases, however, has been generally more gradual than is usual in "postinfectious polyneuritis".

A third clinical group of cases have been reported with mononeuropathies or mononeuropathy multiplex similar to the peripheral nerve involvement associated with polyarteritis. These reports have included eighth cervical or brachial root palsy (188), ulnar nerve palsies (64, 103), bilateral wrist drop (71), bilateral hypesthesia over lumbar dermatomes (158), bilateral sciatic nerve palsies (39), and peroneal nerve palsy (138). Mononeuropathies have also been suggested by patients described with monoplegia and reflex loss (115) and with atrophy of the dorsal hand musculature (115). Combinations of central and peripheral lesions

ay be too confusing to allow classification 103); for example, a patient has been reported ith hypesthesia below the elbows, patchy pesthesia of legs, and symmetrical distal eakness limited to the arms, an extensor antar reflex, and an albuminocytologic dis-ciation in spinal fluid (180).

Pathological studies have been reported on n cases; five are excellent clinical and path-ogical studies of patients with predominantly otor neuropathy with albuminocytologic dis-ciation. The patient reported by Goldberg 6) is of particular clinical interest, since the tient had a pure motor neuropathy starting arms and then affecting legs; paralysis im-oved only to be followed by two severe ex-erbations in which sensation was also affected. stmortem studies showed loss of myelin in ripheral nerves, in anterior and posterior ots, and in posterior columns: occasional rivascular lymphocytes and proliferative end-eritis were present in peripheral nerves. eptinstall and Sowry (87) in a case with sen-y and motor polyneuropathy found similar rivascular infiltrates around perineural blood sels; they also found intimal thickening with lusion of one small vessel. Bailey et al (10) orted pathologic studies of two cases with yneuritis. One showed degeneration of roots h no evidence of vascular disease within vessels: the other showed lesions typical of arteritis with neutrophiles within vessel ls, and there was necrosis and occlusion of ll arteries within nerves. In a patient who been recovering for one year from a sub-te polyneuropathy, Scheinberg (177) found vascular lesions in peripheral nerves but orted axonal degeneration and amorphous erial spreading the fibers. Similar amorphous erial within peripheral nerves was found Tyrer (204) associated with Schwann cell iferation, fibrinoid degeneration of peri-al collagen and myelin loss. Less exten-pathological reports have been made by (88) who found polyarteritis in a case of with "peripheral neuritis," and Contador allero et al (39) who found no abnor-ties in peripheral nerve of a patient with eral sciatic palsies although fibrinoid de-ration was present in the leptomeningeal ls. In nerve biopsies from patients with cute sensory and motor polyneuropathies, Lewis (113) reported a sural nerve biopsy showing loss of axis cylinders and myelin sheaths with replacement fibrosis but no abnormalities of blood vessels, Anderson (5) reported arteriolitis and a perivascular polymorphonuclear cell reaction with extensive demyelination, and Siguier et al (189) found no abnormalities.

In the present series two patients had clinical signs of radiculopathy or neuropathy. One patient (Case 1) had a hypesthesia over the sixth to eighth left cervical dermatomes during the last weeks of life, but peripheral roots and peripheral nerves were not examined at autopsy. The following patient had both CNS manifestations and a peripheral neuropathy which, unlike previously reported autopsied cases, was primarily a sensory neuropathy.

Case 5

This 17-year-old schoolboy developed a butterfly rash followed by recurrent fevers and arthralgias at age 15. Cortisone was started. Three months later he was admitted to the hospital acutely ill with a temperature of 104.6 degrees F. and bilateral pleural effusions. Staphylococcus aureus was grown from sputum; L.E. preparations were positive. The pneumonia cleared, and over the next two months the cortisone dosage was reduced. During this reduction he transiently developed headaches and severe paranoid delusions; neurological examination was normal. Four months later he again developed staphylococcal pneumonia followed by a similar psychotic episode when the dosage of cortisone was further reduced. One week after his second psychotic reaction he complained of numbness in his fingers and feet and had difficulty initiating urination, but no sensory deficit could be found on examination. Symptoms increased for two weeks until he developed acute urinary retention. Repeat examination showed decrease in pain and touch sensation in fingers and both legs to the midcalf. Tendon reflexes were absent in the legs, and the right plantar reflex was extensor. Abdominal reflexes were absent. Cystometrogram showed a totally atonic bladder. Three months later the extensor plantar reflex was no longer present, but the distal sensory loss and atonic bladder persisted over the final 6 months of life without change. He succumbed to a third episode of staphylococcal pneumonia.

Postmortem examination showed bilateral bronchopneumonia and chronic pyelonephritis. There was widespread fibrinoid degeneration of

pelvis of kidney

vessels, verrucous endocarditis, wire loop lesions of kidneys, onion skin lesions of spleen, and focal necrosis of lymph nodes. The brain weighed 1360 g. There was slight thickening of the leptomeninges over the frontal lobes and base and moderate dilatation of ventricles. The spinal cord appeared grossly normal.

Microscopic examination of the brain showed no abnormalities except a general prominence of small blood vessels in the cerebral cortex with an increase in perivascular microglia. The brainstem showed marked perivascular infiltration with lymphocytes and histiocytes. These infiltrates were most frequent in the tegmentum of the mid-brain, and none were found in the substantia nigra or pyramids. Infiltrates in the pons were limited to the dorsal area and in the medulla to the area postremata. In the basal ganglia there were some perivascular lymphocytes under the ependymal surfaces in the thalamus, caudate nucleus, septum pallicidum and corpus callosum. Inflammatory cells were not found within the vessel walls.

Examination of the cervical cord showed some perivascular infiltrations in the upper cervical cord, but none below the mid-thoracic level. Myelin stains of the spinal cord show no abnormalities, but fat stains showed minimal evidence of myelin breakdown in the posterior columns and the dorsal and ventral spino-cerebellar tracts. Peripheral nerves showed a loss of myelinated fibers distally with some evidence of regeneration. Surrounding some of the small vessels within peripheral nerves there were collections of lymphocytes and plasma cells, but no evidence of disease within these vessel walls could be seen. Sections of muscles showed denervation atrophy and focal lymphocytic infiltration. There was fibrinoid change in the walls of small intramuscular blood vessels resembling those seen in the tissues other than the nervous system.

6. Movement Disorders. A variety of movement disorders have been described as unusual neurological manifestations of SLE. Cerebellar ataxia has been observed, but in each case it has been associated with signs of brainstem or corticospinal tract disease suggesting lesions of cerebellar tracts rather than cerebellar cortex (10, 34, 85, 176, 180). An infarct in the left restiform body was found in the one reported neuropathological study (10). Tremor also has been reported; Seminario and Pessano (182) described four patients with SLE who developed "cigarette rolling" tremor with rigidity resembling paralysis agitans. Poch (158) and Willoughby et al (216) have both described cogwheel rigidity without tremor; the latter case showed multiple areas of encephalomalacia in the basal ganglia at autopsy.

One of the most interesting cerebral manifestations of SLE is choreoathetosis; 26 reported cases were found. The majority were described as resembling the chorea of rheumatic fever (Sydenham's chorea) (3, 10, 14, 18, 25, 30, 34, 41, 53, 70, 72, 78, 80, 111, 151, 153, 170, 176, 188). One patient's chorea occurred with pregnancy ("chorea gravidarum") and was reported to resolve following a therapeutic abortion (134); other patients have shown predominently athetoid movement disorders (81, 152), and in one patient chorea was associated with ballistic movements (58). Localized movement disorders including unilateral chorea and athetosis (111) and choreoathetosis limited to the arms (158) have also been described.

Neuropathological studies of seven patients with chorea have been reported. Tumulty and Harvey (203) found old and fresh petechial hemorrhages throughout the brain of a patient with terminal chorea. Glaser (72), Fejer and Tariska (58), and Bauer et al (14) each described multiple small infarctions with thrombosis of small arteries, but in the latter case there was also evidence of rheumatic heart disease. In a patient with chorea five years before death Berry and Hodges (18) found recent and old encephalomalacia associated with proliferative vascular lesions and thrombotic occlusions of leptomeningeal and parenchymal vessels. A patient reported by Bailey et al (10) had chorea six months before death, but infarcts were found only in the brainstem and cerebral findings were limited to a thickening of small arteries. Lessof's (111) case with right hemichorea had subpial blood over the left paracentral lobule but no significant evidence of parenchymal disease.

In the present series movement disorders were not prominent in any patients. One (Case 1) had a transient left-sided cerebellar ataxia and another (Case 2) had a transient pill-rolling tremor of the right hand during a terminal coma secondary to a large intracerebral hemorrhage. In these cases no pathological abnormalities were found in the basal ganglia or substantia nigra, although there were wide-

spread small areas of infarction in the cerebral cortex, cerebellum, and brainstem.

7. Autonomic Disorders. Except for early Soviet studies reporting inflammation and "dwarfing" of neurons in sympathetic ganglia (47, 210, 211) pathological studies of the peripheral autonomic nervous system in SLE are lacking. Raynaud's phenomenon is presumed to be a disorder of peripheral vascular innervation, but its pathological basis is unknown. Poch (158) described a patient with exophthalmus and midriasis and postulated a lesion causing "cervical sympathetic stimulation."

Disorders of hypothalamic function have not been reported in SLE. Klauman and Ben-Efraim (100) reported a patient with hypothermia and coma, but myxedema coexisted with SLE, so hypothalamic disease was not implicated. The following patient, however, had a transient episode of profound hypothermia, hypotension, bradycardia, and somnolence which suggested a disorder of the posterior hypothalamus.

Case 6

This 38-year-old woman had a 5-year course of SLE preceded by discoid lupus of 10 years' duration. Her first admission followed four months of recurrent arthralgias, myalgias and fever. She had a temperature of 104.6 degrees F., erythema nodosum on the legs, lymphadenopathy, edema, albuminuria, leucopenia, anemia, impaired liver function, and a positive Coombs test. Over the next two months arthritis, hepatosplenomegaly, and recurrent fever developed, and L.E. cells were demonstrated. During an examination three months later she suddenly had a generalized convulsion. Postictally she was drowsy, but neurological examination, lumbar puncture, and electroencephalogram were normal. One month later coincident with an exacerbation of fever and arthritis she suddenly developed severe hiccups and diplopia. A left abducens palsy and left extensor plantar response were found. On the following day cortisone was started with prompt defervescence. But she was noted to be lethargic. On the second day of treatment temperature fell precipitously to 93.4 degrees F., pulse to 40, and blood pressure from 120/70 to 80/40. She slept almost continuously but was aroused easily. When awakened, she was alert and oriented with no complaints. This state, reminiscent of hibernation, continued for 4 days and then mental status, temperature, pulse and blood pressure gradually returned to normal. A lumbar puncture showed normal pressure, five lymphocytes/mm³, and a protein of 60 mg/100 ml. Within a week full abduction of the left eye returned, but nystagmus of the left eye on lateral gaze and the left Babinski reflex persisted for the next month. She continued to take cortisone, and although anticonvulsants were never given, seizures did not recur. Her mental and neurological status remained normal until her death from pneumonia four years later.

Postmortem examination revealed lobar pneumonia, obliterative pericarditis, pleuritis, perisplenitis, and wire loop lesions of the kidneys. The brain weighed 1320 g and was grossly normal.

Microscopic examination of CNS revealed an old infarct in the right caudate nucleus and a recent small infarct in the right globus pallidus. There was ferrugination of vessels in the basal ganglia, but no vascular occlusions were found. There was suggestion of abnormal prominence of small vessels. Serial sections of the hypothalamus showed no abnormalities.

8. Disorders of Mental Function. If the confusional state accompanying fever and the anxiety or despondency accompanying any chronic debilitating disease are included, certainly almost all patients with SLE would be found to have disorders of mental function. However, many patients have episodes of clearly psychotic behavior, and these represent one of the commonest CNS manifestations of SLE. In the original writings of Kaposi (95) and Osler (146) delirium and delusions were described; by 1960 one review of psychoses with SLE included 227 cases (59). The frequency of psychosis varies greatly in different series: in psychiatrically oriented studies incidences of 52 percent by Brody (22), 52 percent by O'Connors (143), and 49 percent by Stern and Robbins (195) are reported; whereas in the large medical series Harvey et al (84), and Dubois and Tuffanelli (57) report 15 percent and 12 percent of patients with one or more psychotic episodes.

Disturbances of mental function in SLE take a variety of forms. Confusional states are frequent but are not distinct from the beclouded consciousness and disorientation observed in many diseases (46, 94, 165, 178, 207). However, acute delirium with disorientation, disturbances of attention, delusions, hallucinations, and often excessive motor activity and paranoia, less common in other systemic diseases, are remark-

ably frequent in SLE (7, 28, 33, 36, 58, 59, 72, 81, 90a, 125, 127, 136, 140, 142, 146, 149, 158, 168, 177, 180, 181, 195, 198, 199, 201, 205, 213, 221). Less frequently dementia, a general deterioration of intellectual function and failing of memory, has been described (19, 34, 46, 58, 74, 105, 116, 142, 148, 199).

The above syndromes are those usually associated with organic brain disease, but psychoses generally regarded as "functional," i.e., affective and schizophrenic reactions, appear to be equally common. Shearn and Pirofsky (187) considered depression the commonest mental change, but these may not all have represented psychotic depressive reactions. In 40 unselected patients with SLE O'Connor (143) found psychosis had occurred in 21; 11 were classified as "acute brain syndromes" and 10 as "functional" including 7 with schizophrenic and 3 with depressive reactions and in a subsequent series of 75 patients followed until death he found "brain syndromes" in 39 and psychoses in 45 (144). Stern and Robbins (195) in a similar series found 26 of 53 patients had had psychoses; 7 were considered organic, 8 mixed, 6 schizophrenic and 2 depressive and of the 27 nonpsychotic patients 8 had had depressive reactions. Although O'Connor and Muscher (144) felt an element of "organicity" differentiated the schizophrenic reaction in SLE, most observers have not found them distinct from other schizophrenic reactions. Typical paranoid (27, 50, 121), catatonic (55, 74, 90a, 121, 202), and hebephrenic (81) forms have been described.

The postulated mechanisms include prepsychotic personality (22, 124, 200), toxic effects of SLE, cerebral lesions, and, in some cases, the effect of steroids. Various combinations of these factors undoubtedly are operative in the pathogenesis of these psychoses, but demonstrable cerebral lesions are consistently present. In O'Connor's series (143), where psychoses considered "organic" and "functional" were of about equal frequency, 10 of 11 autopsied cases had neuropathological abnormalities. Because of the frequency of other neurological diseases accompanying mental changes, very few neuropathological examinations of patients with purely psychiatric disease have been reported. Only 5 reported neuropathological studies of psychotic patients lacking other recorded neurological findings were found; 4 had miliary microinfarcts and thrombosis of small vessels (27, 46, 121) and one had multiple cortical ring hemorrhages (72).

Eight of the 24 patients in the present study had mental disorders; and in 7 these accompanied other nervous system manifestations (including Cases 1, 4, 5, and 6 above). Three patients had mild affective disorders, characterized by euphoria in the terminal phase of disease in Cases 1 and 13 and by a transient flattened affect associated with an exacerbation of disease in Case 6.

Five patients had gross psychoses resembling schizophrenic reactions; three persisted until death and two were transient. One patient (Case 5) had two transient episodes of paranoid delusions and another (Case 15) had a very transient psychotic episode, which was temporally associated with increased activity of disease or therapy. This latter patient had a sudden onset of flattened affect, literal thinking and suspiciousness requiring hospitalization on the disturbed psychiatric ward, where a diagnosis of schizophrenia was made. Three days later, however, she suddenly became appropriate and remained normal for the remaining four months of life except for a terminal delirium associated with uremia. At autopsy many small microglial nodules associated with small vessels were found: these were most prominent in the brainstem but were also present in cerebral cortex and cerebellum.

Severe persistent psychosis resembling both hypomania and delirium was illustrated in Case 4. After a 3-year course of SLE, another patient (Case 8) suddenly became psychotic without apparent exacerbation of disease or institution of steroids. She exhibited a flight of ideas and began talking euphorically to God about having achieved sublime happiness. A psychiatrist considered her to have typical acute schizophrenia, however, shortly after his examination she had a generalized convulsion. She remained psychotic for the remaining six weeks of life converting to a mute catatonic state. The pathologic findings were similar to the above cases with multiple microglial nodules in cerebral cortex and brainstem. A marked prominence of small vessels was found with thinning of surrounding parenchyma and increase in perivascular microglia.

The following case is presented in more detail

since a variety of psychiatric and neurologic manifestations were observed.

Case 7

This 24-year-old woman, who had SLE for four years, manifested multiple psychiatric and neurological abnormalities during the last two years of life. At age 21 she began having fatigue, weight loss, and migratory arthritis; over the next year she developed a butterfly rash, lymphadenopathy, leucopenia, and anemia. Retinal hemorrhages and exudates developed, although the blood pressure and renal function remained normal. Hyperactive tendon reflexes in the legs with bilateral ankle clonus were found, but plantar reflexes were flexor. ACTH was started. After ten days of treatment she became acutely agitated with hostile, suspicious behavior, excessive concern with her personal appearance and outbursts of screaming and kicking. ACTH was stopped, and the acute psychosis quickly cleared. ACTH was then reinstituted and maintained for the next two months without recurrence of mental symptoms. Because of a remission of her disease, ACTH was again discontinued. Two months later she was admitted to the psychiatric service after a suicidal attempt. She was severely depressed with insomnia, anorexia, and agitation; this slowly improved. Electroencephalogram was normal. Because of an exacerbation of fever, arthritis, and pleuritic pain two months later, ACTH was given for 17 days with improvement of systemic symptoms and no mental changes. There was no change in the blood pressure and only slight weight gain, but she suddenly had a generalized convulsion the day after treatment was discontinued. She was lucid shortly after the seizure, and a neurological examination was normal. On the following day, however, she had hallucinations and severe paranoid delusions; intermittent diplopia resulting from a loss of convergence was also present. A lumbar puncture disclosed normal spinal fluid with no cells and a protein of 25 mg/100 ml; an electroencephalogram showed paroxysms of 3/sec. slowing. Over the next three days both the psychosis and the diplopia cleared completely. ACTH was resumed and continued until her death one year later. On the day on which therapy was restarted and eight days after the convulsion, she suddenly developed some difficulty in understanding commands and naming objects and was found to have complete acalculia, alexia, and agraphia. She remained alert and oriented, and there were no other abnormal neurological findings. The electroencephalogram was unchanged. This disorder of visual-verbal function cleared over the next two weeks, but one month later she had a second generalized convulsion. A lumbar puncture at that time showed a normal pressure; the fluid contained no cells but a protein of 122 mg/100 ml. The electroencephalogram was unchanged. Although after the seizure the neurological abnormalities were limited to hyperactive tendon reflexes, within ten days she developed bilateral extensor plantar reflexes and loss of abdominal reflexes; these changes persisted during the last ten months of life. During the next eight months her mental status remained relatively normal except for one brief period of flattened affect with paranoid delusions. There was no recurrence of seizures, and no new neurological abnormalities developed. The systemic disease progressed with recurrent fever, increased rash and mucous membrane ulcerations; albuminuria appeared for the first time. Her final admission was precipitated by sudden psychosis with press of speech, tangential associations, and flight of ideas; she was intensely paranoid, often shouting, spitting, and throwing objects at visitors and hospital personnel. During the last 72 days of life she remained psychotic and gradually became less responsive with severe cachexia and ulceration of the skin with abscess formation and septicemia. One month after admission she had another generalized convulsion, and the tendon reflexes were more active in the right limbs thereafter. At no time did she develop azotemia or hypertension; L.E. cells were demonstrated.

Postmortem examination disclosed gangrenous ulcerations of the skin, bronchopneumonia, and abscesses in the kidneys. There were wire loop lesions of the kidneys, onion skin lesions of the spleen, and widespread fibrinoid degeneration of vessels. The brain weighed 1250 g and was grossly normal except for slight thickening of the frontal meninges.

Microscopic examination of the central nervous system showed a generalized prominence of small arterioles and capillaries particularly in the white matter of the frontal lobes. There was an increase of microglia around capillaries in the brainstem. One microinfarct was found in the cervical spinal cord.

C. Spinal Fluid and Electroencephalographic Findings

Cerebrospinal fluid and electroencephalographic abnormalities are common in SLE and are sometimes present even in the absence of neurological signs or symptoms (38, 98, 112, 214). For example, Harvey et al (84) summarized results of spinal fluid examinations on

30 patients; in 22 patients with neurological abnormalities spinal fluids were abnormal in 10, whereas 1 of 8 from patients without neurological findings was abnormal. An additional 88 detailed reports of spinal fluid examinations from patients with neurological complications of SLE were compiled from the literature; 42 (48%) showed proteins over 50 mg/100 ml, and 28 (32%) had pleocytoses of over five cells. Proteins over 100 mg/100 ml have seldom been reported except in cases with neuropathy or myelopathy; however, Fulton and Dyken (66) reported a protein of 806 mg/100 ml in a patient with convulsions and postictal hemiparesis, and Vejjajiva (206) reported a protein of 705 mg/100 ml without pleocytosis in a patient who presented with only headache, stupor, and nuchal rigidity. Only nine case reports were found with pleocytoses in excess of 50 cells in the absence of bacterial or fungal meningitis. One case of myelitis has been recorded with 16,000 cells (61) and a case with confusion and cogwheel rigidity has been reported with 800 cells (216). In both cases cells were predominently polymorphonuclear cells, yet no evidence of meningitis was found at autopsy. In most cases marked pleocytoses have been predominantly lymphocytic (52, 55, 65, 106, 145, 165).

Spinal fluid abnormalities in the absence of neurologic signs can be striking; Pierce and Logothetis (155) reported a patient with a chronic headache and no abnormal signs whose spinal fluid had a protein of 160 mg/100 ml and 104 white cells/mm³, and Villapando and Mendoza (208) presented a similar case whose spinal fluid pressure was 270 mm without elevated protein or pleocytosis. Elevated pressure has also been reported by others (84, 140, 177, 207).

One or more CSF examinations were made on 11 patients in this series. These often followed seizures so findings of elevated pressures were probably of little significance. Protein was elevated in eight patients (ranging from 52 mg/100 ml to 192 mg/100 ml), normal in two, and fluid was grossly bloody due to intracerebral hemorrhage in one. Pleocytosis was present in only two cases (5 and 7 lymphocytes).

Electroencephalographic findings have generally been of little diagnostic or localizing value. Even in patients with clear lateralizing signs or seizures diffuse bilateral slowi been the most frequent finding. Spikes only rarely been reported (12, 13, 34, Electroencephalograms were performed o patients in this series of whom seven ha convulsions; in three cases they were (including the patient without seizure three there was diffuse slowing, and i there were bilateral paroxysms of 3/sec activity.

In summary the spinal fluid often show nificant elevation of protein and in some a mild lymphocytic pleocytosis. Electroen alographic findings are non-specific and commonly show diffuse slowing suggesting spread cortical disease.

D. Effects of ACTH and Corticosteroid Neurological Manifestations

The effect of ACTH and adrenal steroi the neurological manifestations of SLE is ficult to determine because of the diversi complications and their frequent transien ture. Coma (132), encephalopathy (206) creased intracranial pressure (208), cr nerve disorders (160), hemiparesis (65, 66, myelitis (77), neuropathy (5, 53, 97, 113), chorea (25, 53) have all been reported to disappeared or improved subsequent to the Dubois and Tuffanelli (57) reported recove three of five peripheral neuropathies on ste However, the natural history of any of disorders is characterized by spontaneou covery so the relationship of recovery to ment is tenuous. In the present series 15 tients recevied ACTH or cortisone, but instances this was only given during the 7 days or weeks of life. Of the ten instanc cranial nerve disorders seven evolved while patients were receiving treatment; in Ca development of signs was temporally re to a discontinuation of ACTH, but in no was improvement clearly related to the stitution of treatment. Furthermore, the of severe paraplegia and peripheral neurop clearly deteriorated while on treatment, the case with an apparent hypothalamic drome developed her symptoms two days beginning cortisone. Certainly, no efficacio adverse effect of steroids on these neuro manifestations were apparent in this series.

The effects of treatment on convulsive

mental disorders pose different problems. There is experimental and clinical evidence that steroids lower the seizure threshold (73), and their production of psychoses is well recognized (162). Therefore, seizures and psychoses are sometimes regarded as complications of therapy. Soffer et al (193) considered the incidence of convulsions greater in patients receiving cortisone or corticotropin. In 18 patients with seizures Harvey et al (84) related 5 to steroid treatment. Dubois (52) considered steroids as a cause of seizures in 3 of 19 patients with convulsions, but, conversely, he noted improvement of convulsive disorders in others (55, 56). Furthermore, Brunsting et al (24) described the dramatic interruption of status epilepticus by cortisone. The apparent control of recurrent convulsions (55, 56, 88, 125, 164) and the improvement of electroencephalogram abnormalities (156, 192) have also been described. Indirect evidence for the role of steroids in seizures is the incidence of seizures before and since the widespread use of steroids in SLE. As noted above, the frequency of seizures in SLE has not changed since 1950, so any adverse effects must be slight or counterbalanced by beneficial effects.

In the present series only six of the 13 patients with seizures were receiving cortisone or ACTH at the time of their initial seizure; conversely, seven of the 11 seizure-free cases received therapy. Case 3, an epileptic since infancy, had no accentuation of seizures when cortisone was instituted, and Case 6 who had a single seizure prior to treatment never had a recurrence while on cortisone. The only apparent temporal relations of seizures to change of medication occurred in one patient (Case 6), whose seizure occurred during reduction in dosage. Thus, in this series no enhancement or suppression of seizure activity by steroids was apparent; convulsive disorders did not appear to be a direct complication of treatment in any case.

Mental disorders present a perplexing problem since a significant number of patients receiving steroids or ACTH for whatever cause develop psychoses, and a significant incidence of psychoses was well recognized with SLE prior to their introduction. The efficacy of cortisone or corticotropin in reversing the acute confusional states or delirium accompanying exacerbations of SLE is well documented (21, 116, 125, 178, 192, 193, 194). The problem of causation arises with the development of affective or schizophrenic reactions. Soffer et al (193) noted a 63 percent incidence of euphoria, depression or paranoia in patients with SLE receiving long term cortisone or corticotropins. However, affective and schizophrenic reactions can occur as a manifestation of SLE, and it is the impression of a number of authors that the majority of psychoses are due, not to steroid treatment, but to the underlying disease (21, 116, 144, 195). Characteristic schizophrenic reactions unrelated to steroids are seen in SLE (15, 27, 195), and improvement of affective and schizophrenic reactions with steroid treatment has been reported (74, 110, 153, 168, 213). The clinical form does not appear of help in differentiating steroid and SLE induced psychoses.

In the present series two psychoses characterized by psychiatrists as typical schizophrenia occurred in patients who were not receiving steroids or ACTH. The remaining three schizophrenic reactions occurred while on therapy and in two instances appeared related to the institution of treatment. The extreme difficulty of determining whether steroids or the underlying disease was responsible for the psychoses was exemplified in Case 4 where a psychosis accompanying the introduction of steroids coincided with increased disease activity, in Case 5 where the psychosis was related temporally to a reduction in dosage, and in Case 7 where a psychotic episode in a patient on long term ACTH therapy occurred independent of any change of dosage or obvious exacerbation of disease.

It does not appear that a psychotic episode is a contraindication to steroid treatment; only by clearly relating improvement or deterioration of mental status to steroid dosage in the individual patient can its role in mental changes be postulated.

IV. THE NEUROPATHOLOGICAL ASPECTS

A. Nature of the Lesions

Although lesions in the nervous system have often been described in SLE, there is still uncertainty as to what constitutes the characteristic neuropathological changes in this disease. Most reports have dealt with single autopsies or relatively small numbers of cases. The largest

detailed neuropathological study is that of Glaser (72), who found lesions in brains in three out of six cases.

Kaposi (95) examined the nervous system in some of the patients in his original description of the disease, but he recorded only gross atrophy. The first reported histological examinations were by Davidovsky (47) and Wail (210, 211) in Russia, but their primary interests were in changes in autonomic ganglia. They speculated that the symmetry of systemic lesions must be controlled by the brain via the autonomic nervous system. Wail (211) did, however, describe brainstem hemorrhages similar to those in Case 13 of this series. The first discerning study was that by Jarcho (92) in 1936; he found occluded small vessels with microinfarcts in a patient who had had no clinical neurological abnormalities. Since then small infarcts with small arterial or arteriolar occlusions have frequently been reported (6, 14, 18, 27, 37, 46, 58, 61, 72, 75, 90a, 114, 121, 123, 136, 137, 177, 198, 213); and in a few instances there were venous occlusions (6, 61, 66, 195). The findings in many of the cases in the literature are vague or non-specific, but over one-half of the reports describe infarcts or hemorrhages, often microscopic in size.

Significant gross abnormalities were found in only 10 of the 24 patients in this study (Table 5). These included three cases with large intracerebral hemorrhages, one with multiple pontine hemorrhages, two cases with multiple small fresh hemorrhages, four with small areas of old infarction, and one with a small subpial hemorrhage which was an incidental finding. Lesions were far more common microscopically; microinfarcts or increased pericapillary microglia were found in 20 of the 24 cases. Microinfarcts often consisted of nothing more than a small cluster of pleomorphic histiocytes, the so-called microglial nodules. For example, in one patient (Case 19) seven such infarcts were found in a single section of the medulla oblongata, yet they were so small that they caused no clinical symptoms and could easily be overlooked on cursory microscopic examination. The regular occurrence of minute infarcts in this and previous neuropathological studies suggests that SLE of the nervous system is, in most cases, a vascular disease involving very small vessels.

Libman and Sacks (115) suggested that the neurological signs in SLE might be due emboli from verrucous endocarditis, and explanation was supported by Adams Michelsen (2). The only case in which emb have been demonstrated in cerebral vess was in a patient with verrucous endocard reported by Albertini and Alb (4); in that there were also embolic lesions in the kidn spleen, and coronary arteries. In most ca however, embolic infarction is usually found in other organs, and endocarditis occ considerably less frequently than cerebral croinfarcts. Furthermore, in the present se there was no consistent relationship betw cerebral lesions and endocarditis. Therefore most cases cerebral lesions are not on an emb basis; instead, cerebral microinfarcts hemorrhages must be due to an intrinsic order of cerebral vessels. The exceedingly s size of most infarcts and the occurrence of p capillary microglia proliferation suggest the underlying pathological process in the bl vessels of the nervous system affects mainly small arterioles or capillaries. However, on viewing the literature or studying the pre cases a single or distinctive lesion of the ve cannot be found. In both this study and prev reports there is evidence of inflammatory, structive, and proliferative cerebrovasc changes (Table 5).

The assumption is often made that the le is inflammatory, yet true arteritis of cere vessels has been a rare finding (18, 35, 52, 132, 157, 177, 190). On the other hand, vascular infiltrates of inflammatory cells frequently been noted (6, 14, 58, 61, 64, 72 121, 129, 145, 150, 175, 195, 204, 213), but significance is unknown. True vasculitis inflammatory cells within the vessel wall found in only 3 of the 24 cases in this st and in none of these cases was it a promi or generalized phenomenon. In Case 2 th flammatory reaction was almost entirely vascular and localized to subependymal a Adjacent to the intracerebral hemorrhag that case there were occasional polymor nuclear cells within vessel walls; these cha were more consistent with a secondary rea to the intracerebral and subarachnoid he rhage than with primary vascular disease Case 10 a few polymorphonuclear cells found within the walls of both arterioles

TABLE 5

Summary of Clinical-Pathological Findings

Case No.	Age and sex	Duration of disease in years	Neurological findings		Neuropathological findings							
			Interval between onset of neurological disease and death	Signs and symptoms (Mode of death in parentheses if non-neurologic)	Gross	Microscopic						
						Vasculitis	Vascular necrosis	Fibrin thrombi	Micro-infarcts	Microhem-orrhages	Perivascular microglia	Perivascular infiltrates
1	27F	10	9 yrs.	Numerous transient signs; terminal corticospinal tract signs with death in status epilepticus	Old infarct, left caudatoputaminal junction; many small acute hemorrhages	0	+	+	+	+	+	0[1]
2	49F	6	6 yrs.	Recurrent focal seizures and terminal intracerebral hemorrhage	Fresh hemorrhage, right parietal lobe; old hemorrhage, right parietal-occipital area	+	0	0	0	0	+	+[1,3]
3	23F	8	7 yrs.	Transient left oculomotor nerve palsy (heart failure)	None	0	0	0	0	0	+	0[1]
4	43F	1.5	1 yr.	Paraplegia and psychosis (pulmonary embolus)	Old infarct, genu of left internal capsule. Irregular discoloration of spinal cord	0	0	0	+	0	0	0[1]
5	17M	2	9 mo.	Peripheral neuropathy and psychosis (pneumonia)	Mild dilatation of ventricles	0	0	0	0	0	+	+[1]
6	38F	5	5 yrs.	Single seizure, transient 6th nerve palsy, and episode of hypothermia, bradycardia, and hypotension (pneumonia)	None	0	0	0	+	0	0	0[1]
7	24F	4	2 yrs.	Multiple psychotic episodes, corticospinal tract signs, and transient loss of convergence (septicemia)	None	0	0	0	+	0	+	0[1]
8	34F	4	6 wks.	Severe psychosis and seizures (septicemia)	Thickened leptomeninges	0	0	0	+	0	+	0
9	24F	7	4 days	Deafness followed by coma with ophthalmoplegia and bilateral corticospinal tract signs	Large right frontal intracerebral hemorrhage and many small hemorrhages in corpus callosum	0	+	0	+	+	+	0[2,3]
10	16F	0.8	5 days	Sudden scotomata with retinal hemorrhages and death in status epilepticus	Many 1-3 mm. hemorrhages in lower cortical layers	+	+	+	+	+	0	0[2]
11	18F	2	6 wks.	Recurrent seizures with residual left hyperreflexia. Coma during terminal 3 wks. with papilledema, hemiplegia, and a transient right-sided tremor	Large right fronto-parietal intracerebral hemorrhage	+	0	0	+	0	0	0[4]
12	25F	1.5	12 days	Right internuclear ophthalmoplegia and skew deviation. Terminal seizure. (pericardial effusion and pulmonary edema)	Infarct in left basis pontis	0	0	0	+	0	+	0[4]
13	24F	2	3 wks.	Stupor with dysarthria followed by right supranuclear facial palsy and coma	Multiple hemorrhages in pons extending into midbrain	0	+	+	+	+	+	0[2]

TABLE 5—*Continued*

Case No.	Age and sex	Duration of disease in years	Neurological findings: Interval between onset of neurological disease and death	Neurological findings: Signs and symptoms (Mode of death in parentheses if non-neurologic)	Neuropathological findings: Gross	Neuropathological findings: Microscopic: Vasculitis	Vascular necrosis	Fibrin thrombi	Micro-infarcts	Microhemorrhages	Perivascular microglia
14	24F	1	6 wks.	Recurrent Jacksonian seizures, weakness in right leg, and right hyperreflexia (uremia)	Small infarct in left frontal lobe	0	0	0	+	+	+
15	34F	2	4 mo.	Schizophrenic reaction unassociated with treatment lasting 3 days (uremia)	None	0	+	0	+	+	+
16	23F	2	1 yr.	Single left-sided seizure (heart failure)	None	0	0	0	+	0	0
17	21F	0.3	1 day	Two seizures (uremia)	None	0	0	0	+	0	0
18	18F	2	1 day	Terminal seizure (pneumonia)	None	0	0	0	+	0	0
19	26F	0.2		None (pneumonia)	Recent small subpial hemorrhage	0	0	0	+	0	0
20	29F	0.6		None (pneumonia)	None	0	0	0	+	0	0
21	33F	1		None (heart failure)	None	0	0	0	0	0	0
22	40F	1.5		None (uremia)	None	0	0	0	0	0	0
23	23M	2		None (pneumonia)	None	0	0	0	0	0	0
24	29F	5		None (constrictive pericarditis and pneumonia)	None	0	0	0	0	0	0

[1] Details of clinical disease and pathological findings in text.

[2] Hemorrhages occurred in absence of hypertension or thrombocytopenia.

[3] Typical brain purpura was found in addition to many microinfarcts in cortex, cerebellum, and brainstem.

[4] Vasculitis found in a single vessel in addition to non-inflammatory microinfarcts in cortex, cerebellum, brainstem, and spinal cord.

[5] One area of infarction involved right medial longitudinal fasciculus.

[6] Hemorrhages occurred in presence of hypertension, thrombocytopenia, and uremia, but old microinfarcts were also found in the spinal cord.

veins, adjacent to areas of hemorrhagic infarction, and this reaction was also thought to be secondary. In Case 11 the vasculitis was of a different form, for focal necrosis with polymorphonuclear cells was found in one segment of a major branch of a middle cerebral artery. The lesion in this vessel was typical of polyarteritis nodosa, but only one vessel was so affected, and the remainder of the neuropathological changes were similar to those in the other cases.

Destructive changes in the walls of small cerebral vessels have been frequently encountered, and these have been described as fibrinoid degeneration (18, 39, 61, 72, 90a, 121, 126, 129, 145, 150, 157, 175) or as hyalinization necrosis (6, 44, 66, 213). Destructive les were found in cerebral vessels in five case this study. In each case there was necrosi the vessel wall with extravasations of red or fibrin. In Cases 1, 10, and 13, all of w died of acute CNS disease, this was a pro nent finding (Fig. 2 and 3). Fibrin thro were also found occluding small vessels in e of these cases. In Case 13 there was a histor hypertension, and terminally there was a l pontine hemorrhage. In this case the necr of blood vessels might have been the resul hypertensive vascular disease. In Cases 9 15 necrosis of small vessels was also found

FIG. 2. Section of medulla oblongata from Case 1 showing fibrinoid degeneration of a small blood vessel. There is fibrin exudation into the tissue and a surrounding zone of recent necrosis of the parenchyma. Phosphotungstic acid hematoxylin stain, × 210.

much more infrequently (Fig. 4). The vessels involved by the necrosis were generally arterioles or minute prearteriolar arteries. In Case 9, however, there were many foci of pericapillary coagulation necrosis, often with ring hemorrhages typical of brain purpura. The capillary vessels within these lesions showed thickening, eosinophilia, and refractility of the wall resembling fibrinoid degeneration.

Daly (46) first described proliferative changes in intima of cerebral vessels of less than 100 microns in diameter, and similar proliferation or swelling of cerebral endothelial cells has been noted by others (6, 10, 14, 18, 58, 72, 90a, 129, 133, 136, 145, 198, 213). In the present series a prominence of capillaries was an almost universal finding (Fig. 5). Unlike the destructive changes these proliferative changes did not correlate with acute CNS disease and were extremely prominent in several cases with minimal or no neurological disease (i.e. Cases 17, 18, 19 and 23). Although the prominence initially suggested proliferation of endothelial cells, our impression was that it represented thickening of the cytoplasm of these cells. It was not possible to actually quantitate these changes with any accuracy because of variations in fixation, shrinkage artifacts, and the frequent terminal anoxic encephalopathy.

In summary, although lesions of small blood vessels were found in 20 of the 24 cases, there was no single typical or pathognomonic lesion in the brain comparable to the "wire-loop" lesion of the kidney or "onion-skin" lesion of the spleen. The frequent microinfarcts and occasional hemorrhages appeared to result from intrinsic disease of small vessels, predominantly arterioles and capillaries. In cases with acute disease vascular necrosis was found; in almost all cases a prominence of capillary endothelium was apparent. The alterations in blood vessels were not accompanied by inflammatory cells within vessel walls, and, therefore, cannot be classified as a vasculitis in the usual sense.

All of the observed neuropathological changes could be on a vascular basis with exception of the myelopathy (Case 4) and peripheral neuropathy (Case 5) which are discussed below.

FIG. 3. Section of brainstem from Case 1 showing fibrin thrombus in a small blood vessel with surrounding acute necrosis of brain tissue and small recent hemorrhages. Hematoxylin and eosin stain, × 215.

B. Comparison with Other Diseases

Hypertensive cerebrovascular disease is characterized by a similar prominence of small vessels, vascular necrosis, and small areas of infarction. However, with hypertension these changes in small arterioles and capillaries are accompanied by hypertrophy and hyalinization of the media of larger vessels. In acute hypertensive encephalopathy microglial clusters indistinguishable from microglial clusters or microinfarcts seen in SLE are present. In acute hypertensive encephalopathy, however, these lesions tend to be of the same age and there are usually lesions in the larger arteries. Arteriolar necrosis can be seen in both conditions. The frequency of intracerebral hemorrhage in SLE also has suggested a relationship to hypertensive cerebrovascular disease (4, 18, 84, 116, 195, 203). Only one of the three patients in this study who died with intracerebral hemorrhage had any recorded elevation of blood pressure and none had thrombocytopenia. Furthermore, the hemorrhages in all three occurred in frontal or occipital lobes rather than putaminal or thalamic sites where intracerebral hemorrhages associated with hypertension characteristically occur. Intracerebral hemorrh in SLE was explained in one case reported Harvey et al (84) on the basis of rupture o "small aneurysm associated with lupus arteri but no similar observations have been made others. Even in hypertension the pathogenesis intracerebral hemorrhage is unknown. Ros blath (169) has postulated that the intracereb hemorrhage is not the result of elevated in vascular pressure or aneurysm formation, rather that the small vessel disease accompany hypertension leads to the hemorrhage. The that in SLE intracerebral hemorrhage appears result from primary disease of arterioles capillaries in the absence of blood pressure ele tion tends to support this hypothesis.

Polyarteritis nodosa more frequently invol the peripheral nervous system but may invo the CNS in about 20 percent of cases (60, 131). In contrast to the vascular lesions in S the lesions of polyarteritis are characterized by intense cellular inflammatory reaction within vessel wall. Furthermore, polyarteritis invol predominantly medium-sized to small arter whereas in SLE the smallest arteries, arterio and often capillaries are affected. There is li similarity of the cerebrovascular lesions in th

FIG. 4. Section of medulla oblongata from Case 9 showing old necrosis of small blood vessel. There is fibrin impregnation of surrounding tissue and increased perivascular microglia. Hematoxylin and eosin stain, × 250.

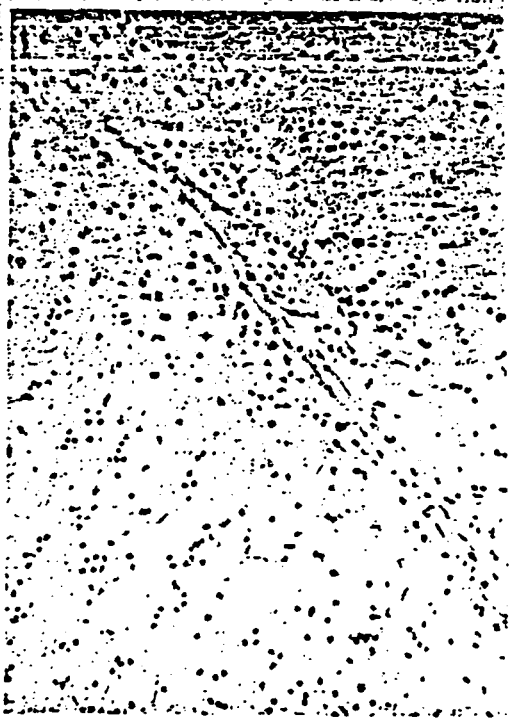

FIG. 5. Section of cerebral cortex from Cas showing prominence of small blood vessels. Cr violet stain, × 110.

two diseases, yet in Case 11 typical polyarteritis was found in the one medium-sized artery, and in Case 1 typical polyarteritic lesions were found in viscera (32), although not in cerebral vessels. Thus, some overlap of pathological findings in the vessels does exist.

Brain purpura was also found in a single case (Case 9) in addition to cortical and brainstem microinfarcts. The lesions of brain purpura are characterized by a pericapillary focus of coagulation necrosis surrounded by pleomorphic histiocytes and often a ring in intact red blood cells (25). They are located in white matter, especially frequent in the corpus callosum and brachium pontis. They are generally associated with acute infections and toxic diseases of many kinds. The cerebral lesions in SLE do not have this characteristic appearance or distribution. The occurrence of brain purpura in a single case in this series probably represents a coincidental finding.

Thrombotic thrombocytopenic purpura (Moschowitz's disease) is characterized by lesions that resemble the vascular changes in SLE in several respects. In this disease Adams et al (1) described hyperplasia of the endothelium of arterioles and capillaries, vessel wall necrosis, occlusions of vessels with acidophilic thrombi, and occasional petechial hemorrhages. All of these were found in our cases of SLE. However, thrombotic thrombocytopenic purpura differs from SLE in being a diffuse and acute disease with widespread obvious changes in small vessels and a paucity of parenchymal disease. In SLE the vascular changes are more subtle; the capillary prominence is less apparent; vessel necrosis, fibrin thrombi and petechial hemorrhage are less frequent; and parenchymal changes (microinfarcts) are prominent. Furthermore, the lesions in thrombotic thrombocytopenic purpura are acute and of the same age, while in SLE the vascular and parenchymal lesions are usually of varied ages.

Acute rheumatic fever has not been well characterized neuropathologically, but some of the changes that have been recorded resemble those found in SLE. Winkelman and Eckel (218) described swelling and proliferation of endothelial cells of arterioles and capillaries of the cerebral cortex and Costero (43) found microglial nodules in the brainstem similar to the microinfarcts found in our cases with SLE. The lesions ascribed to rheumatic arteritis by Bruetsch (23) are, in our opinion, best explained by multiple cerebral emboli.

In *serum sickness* the neuropathological changes in man are even less well defined. There have been two reported studies describing widespread cortical microinfarcts with dilatation, hyalinization, and necrosis of small vessels and perivascular infiltrates (107, 219). Again these are findings that occur in some cases of SLE. Examination of the brains of rabbits with acute serum sickness by one of us (MTJ) showed no lesions resembling those of SLE. Furthermore, after the completion of the present study frozen sections of brain tissues from three patients dying with SLE have been examined with fluorescein-labeled antihuman globulin; no abnormal fixation of human gamma globulins was found in the cerebral vessels. However, none of these patients had acute neurological disease immediately preceding death, so that no conclusions regarding the role of circulating antibody-antigen complexes in the pathogenesis of cerebral vessel changes in SLE can be made. Certainly, an immunological basis for the vascular endothelial changes in SLE seems likely (157).

Although it is not possible to delineate a neuropathological process that is wholly distinctive for SLE, the diagnosis of SLE can be made on neuropathological grounds alone in many of the cases studied. The usual lack of any true arteritis, in the sense of an inflammatory cellular infiltration within the vessel wall, and the absence of pathology in medium-sized and small arteries are features which clearly differentiate the neuropathology of SLE from that of polyarteritis. The observed degenerative and proliferative changes in small cerebral vessels in SLE are not distinct from some of the vascular changes found in hypertensive encephalopathy, thrombotic thrombocytopenic purpura, acute rheumatic fever, and serum sickness. However, the neuropathological lesions of SLE are characterized by their being more focal or scattered than is usual with these disorders and by the fact that they vary in age from region to region, rather than appearing to have occurred simultaneously in many localities.

V. CLINICAL-PATHOLOGICAL CORRELATIONS

In general the clinical neurological manifestations of SLE correlate well with the observed neuropathological findings. The frequency of seizures and cranial nerve dysfunction can be related to the prevalence of microinfarcts in the cerebral cortex and brainstem respectively. During an acute phase of the disease widespread acute vascular lesions may result in gross neurological abnormalities or uncontrolled

seizures as seen in the two patients (Cases 1 and 10), who died in status epilepticus; in both cases vascular necrosis was found with diffuse cortical microhemorrhages. In Case 2 a recurrent convulsive disorder with flickering of light in a homonymous visual field could be related to a subcortical scar in the contralateral visual association area; in Case 14 a recurrent right-sided Jacksonian seizure resulted from an old infarct in the left prefrontal cortex.

The fact that neurological abnormalities are often transient (as seen in Cases 1, 3, 6, 7 and 16) is probably explained by the small size of most of the infarcts. This is best exemplified by the temporary discrete cranial nerve disorders usually resulting from small but strategically located microinfarcts within the brainstem. The correlation of isolated neurological signs with small areas of infarction was best demonstrated in Case 12, where a unilateral internuclear ophthalmoplegia resulted from a small infarct limited to the medial longitudinal fasciculus. The nature of the transient third nerve palsy in Case 3, however, suggested a lesion within the nerve rather than within the brainstem. The presence of pain and the sparing of pupillary function simulated the oculomotor palsies seen in diabetes, where the lesion is presumably caused by occlusion of a nutrient vessel of the nerve. This occlusion results in infarction of the central core of the nerve, which contains the fibers to the extraocular muscles, and spares the subepineurial region where the pupilloconstrictor nerve fibers are located (51).

Although the majority of the neurologic manifestations of SLE can be accounted for by the observed vascular disease, other mechanisms must be considered in several cases. Although the clinical signs of myelopathy corresponded well to the pathological findings in Case 4, the pathogenesis of the spinal cord lesions is unclear. The distribution of lesions in the cord and their histological features resembled subacute combined degeneration, yet there was no evidence of concurrent pernicious anemia, and the clinical evolution of the disease indicated initial involvement of the anterior rather than the posterior columns of the spinal cord. A similar peripheral degeneration of the cord has been described in meningovascular syphilis (122), where occlusion of the peripheral small perforating vessels results in the so-called syphilitic halo. However, in Case 4 an e sive search uncovered no lesions within vessels, so that some mechanism other vascular occlusion must be considered in case.

In the patient with peripheral neurop (Case 5) a non-vascular cause of the n pathological changes must also be consid Although mononuclear cells were found ar blood vessels within the peripheral nerves, was no vasculitis and no vascular occlu were found. Pathologically the findings i peripheral nerves bore more resemblanc those seen in idiopathic polyneuritis (Gui Barre syndrome) than to the vascular lesio nerves found in polyarteritis. Clinically symmetry of the neuropathy also suggest diffuse disease of nerves rather than mu mononeuropathies secondary to neural in tion. The reported clinical syndromes pathological findings in neuropathies assoc with SLE suggest two distinct disease proc In some cases, mononeuropathies secondar vascular disease are found (10, 88). In ot a symmetrical neuropathy evolves with p logical findings suggesting a relationship t Guillain-Barre syndrome (10, 76, 87); suggesting some immunological basis other one mediated via changes in vessel walls previously stated by Bailey et al (10) vascular changes alone cannot account fo neuropathy in all cases.

One cannot help but wonder whether vascular disease alone can lead to the di disorders of mental function observed in At least some of these abnormalities mu on a basis of observable pathoanatomic cha The acute confusional states and delirium ably result from widespread cerebral co disease, and the frequent occurrence of h cinations might suggest temporal lobe inv ment. On the other hand, pathoana concepts are inadequate to explain the sc phrenic and affective reactions that occ SLE. The reactions tend to occur durin acerbations of the disease and are ofter sociated with other neurological abnormal and in all cases of psychosis in this series d lesions related to small vessels were f Nevertheless, whether or not these vascul sions are sufficient to account for the asto ng abnormalities of mental funct n is u tain. Recently in a patient dyi[illegible]rin

acute exacerbation of SLE, a diffuse fixation of homologous immunoglobulins to nuclei was found in many organs including the brain (Kaplan, unpublished data). This unusual finding of globulins was not associated with histopathological changes. A mechanism such as this might account for the acute psychoses in SLE, where the observed pathological changes in the vessels fall short of fully explaining the clinical manifestations.

VI. SUMMARY AND CONCLUSIONS

In analyzing the clinical and neuropathological findings in 24 patients with systemic lupus erythematosus (SLE) and reviewing the previously reported clinical and neuropathological studies the following conclusions have been made:

1. SLE frequently involves the central nervous system (75% in the present study) and only rarely involves the peripheral nervous system (8% in the present study). Although CNS involvement often develops terminally and may cause death from intracerebral hemorrhage or status epilepticus, it may also occur early in the disease and may be mild and transient. Therefore, the development of CNS manifestations per se does not imply a bad prognosis.

2. Convulsive disorders, disturbances of mental function, and signs referable to cranial nerves are the commonest neurological manifestations of SLE (52%, 33% and 42% respectively in this study). The prevalence of microinfarcts in cerebral cortex and brainstem probably accounts for the preponderance of these signs.

3. A wide variety of other CNS signs and symptoms may occur in SLE including hemiparesis, paraparesis, movement disorders, and apparent disorders of hypothalamic function, all of which were observed in this group of patients.

4. Peripheral neuropathy in SLE may take the form of distal sensorimotor neuropathies, of a Guillain-Barre syndrome, or of mononeuropathy. The latter presumably results from vascular lesions within nerves, but the former types, such as the distal sensory neuropathy reported in this series, probably have another basis.

5. The cerebrospinal fluid shows abnormalities in about one-half of the patients with neurological manifestations. Protein content often is moderately increased and a mild lymphocytic pleocytosis may occur. Very high protein contents are found primarily in patients with myelopathies or neuropathies. Electroencephalographic abnormalities are also common but are usually diffuse and non-specific.

6. The effect of steroid treatment on the neurological manifestations is uncertain. It has been claimed to have resulted in improvement in individual cases, but a general beneficial effect could not be discerned in this series. Seizures and mental disorders may, at times, be precipitated or accentuated by steroids, while in other cases steroids bring about improvement in these disorders. The nature of the convulsive or mental disorders induced by SLE does not appear to differ significantly from those precipitated by steroids, so that treatment must be determined by the response observed in the individual patient.

7. Analysis of the neuropathological findings shows predominantly changes related to small blood vessels. Destructive and proliferative change in arterioles and capillaries were found; a true vasculitis cannot be considered to be the fundamental vascular change in the nervous system. The changes in the small vessels are quite different from the vasculitis of polyarteritis nodosa, but do resemble those observed in thrombotic thrombocytopenic purpura and hypertensive encephalopathy, and they may resemble the less well-defined changes in acute rheumatic fever and serum sickness.

8. The localization of vascular changes and resultant microinfarcts in the cerebral cortex and brainstem correlate well with the clinical signs in most cases, and the small size of the infarcts probably accounts for the transient nature of some neurological signs. However, changes in blood vessels alone probably cannot account for the pathological changes found in the spinal cord or peripheral nerves of the cases of paraparesis and sensory neuropathy in this series. Furthermore, the pathoanatomic changes may not fully account for the disorders of mental function seen in SLE.

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