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, Isposi (95) mentioned disturbed cerebral function associated with the disease, which took the form of recurrent delirium in 2 of his 11 patients. Osier (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,
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 analyse 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 1959 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 re-examined 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.

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 LE cell phenomenon was demonstrated in all patients seen after 1950. All patients except one developed arthropy; but gross deformities of joints were rare. Anemia developed in all but one of the patients and leukopenia 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
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

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*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. (50) 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, 33, 74, 79, 81, 107, 133, 166, 175), psychosis (27, 58, 107, 195), hemiplegia (29, 147, 161, 183), encephalopathy (206), neuropathy (74, 88), myelitis (77, 183), chorea (25, 151), diplopia (83, 188), and paresthesias (82, 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 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. Optokinetic nystagmus was diminished with the targets moving to her right.

Electroencephalogram and spinal fluid examination were normal. Albuminuria was present the first time. At age 23 a red, burning butter rash developed. The facial paralysis, left hyperreflexia, and recurrence of anisocoria were the only abnormal neurological findings. One L.E. cell was found on numerous preparations. At age 26 she was admitted because of microscopic hematuria, but renal function studies and blood pressure were normal; the L.E. phenomenon was strongly positive for the first time. All abnormal neurological findings had disappeared except the facial paralysis. Five months later she complained of numbness of the left arm and leg with sparing of the arm and face. Two months after this she was admitted for the 10th and final time with acute right flank pain. Blood pressure increased from 130/80 to 190/100, the hematocrit fell, and a right upper quadrant mass developed; a right nephrectomy was performed with evacuation of a massive subcapsular perinephric hematoma. The blood pressure returned to normal after the operation, and the blood urea nitrogen was 26 mg/100 ml. She complained of generalized weakness and was found to have vertical and horizontal nystagmus; slurred speech, weakness of the right arm, hyposthesia over the left 6th to 8th cervical dermatomes, bilateral hyperreflexia with a brisk jaw jerk, absent abdominal reflexes, and bilateral extensor plantar reflexes. Spinal fluid was again normal. Strength was improving when on the 21st postoperative day left flank pain with a mass an increase in blood urea nitrogen to 120 mg/100 ml, and a rise in blood pressure to 160/100 developed. Corticosteroids were given for the first time. In one week the blood urea nitrogen returned 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

<table>
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<tr>
<th>Neurologic Manifestations</th>
<th>No. Patients</th>
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<tr>
<td>Seizures</td>
<td>12</td>
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</tr>
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<td>Mental disorders</td>
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* One case had idiopathic epilepsy.
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 45 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 (22). 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 4 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, 14, 18, 33, 41, 57, 74, 75, 84, 86, 88, 94, 144, 157, 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 Musnier (144) reported seizures in 30 percent.

Nevertheless, the development of seizures does not necessarily herald death. Montgomery and McClelland (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 (56, 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, 85, 95a, 142, 198). Conversely, recurrent seizure disorders extending over a year or more may develop (72, 84, 135, 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, 138, 137, 159, 199). Terminal Jacksonian seizures, however, have been related to intracerebral hemorrhage (203) and subarachnoid hemorrhage (212). Only one case
has been studied pathologically in which sei-
ures antedated other manifestations of SLE,
and in this case it is significant that no neu-
ropathologic 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-observed
by the recent observations of lupus-like syn-
dromes induced by anticonvulsants. In 1953
Miescher and DeLoreetas (128) attributed
a case of SLE to anticonvulsant medication, and
this association of hydantoin 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 anti-
convulsants have now been implicated by sub-
sequent reports (3, 17, 91, 103, 179, 217). Clinically the syndrome of SLE is typical in-
cluding 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. phe-
nomenon has usually occurred subsequent to the
withdrawal of the drug (3, 17, 91, 103, 162, 174)
and Rallison et al, (162) reported a case in
which a renal biopsy showed "wire loop" le-
isons but a subsequent biopsy 19 months later
(26 months after stopping diphenylhydantoin)
showed no "wire loops." In some instances, how-
ever, apparent drug induced SLE syndrome may
persist or progress even after withdrawal of anti-
convulsants (90, 91, 103). 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
play a 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 con-
volusive disorder since infancy and was con-
sidered to have idiopathic epilepsy; seizures
did not become more frequent or severe with
the development of SLE, despite the appear-
ance of other neurological manifestations and
finding of microinfarcts pathologically. The re-
maining 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-
year before death, respectively, with no recur-
en 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, 13,
12, 17, and 18) had seizures only terminally. In
Cases 17 and 18 terminal seizures were associ-
ated 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 status
in SLE was seen in three patients who develop-
status epilepticus. In Case 11 this was second-
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 cen-
tral 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 di-
sagnosed as erythema multiforme at age 43. A
mid leukopenia and anemia were found, and
shortly thereafter hepatosplenomegaly and ar-
thritis developed. Five months later she had a
generalized convolution. She had pleuritis and
pericarditis at that time, and the L.E. phenom-
emon 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 experi-
enced a flickering of light in her left visual field,
which she compared to the opening and closure
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 pro-
dromata were followed by a generalized motor
seizure. Repeated neurological examinations dis-
covered no abnormality of visual field; there was
a left supranuclear facial weakness and a slight
decrease in motor strength in the left extremi-
ties. Tendon reflexes were symmetrical, but the
LEDMBA has been seen (16, 33, 66, 74, 84, 96, 107, 123, 142) with normal spinal fluid pressure (53, 123, 134) and with increased pressure (66, 90a, 177), and optic atrophy has also been reported (85, 96, 133, 135, 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. (54) 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 (33) 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, 216, 229) signs of SLE. This frequency of association has given rise to speculation on the immunologic nature of both disorders (67, 154, 191, 222).

Lenticular response, although not clearly evi-
dent, 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 ad-
imination.

General postmortem examination showed ver-

nous endocarditis, lupus pericarditis, adhesive pericarditis, onion skin lesions in the spleen, and renal degeneration in vessels. The brain contained 1220 g; there was herniation of the right temporal lobe and compression of the mid-

brain. Within the right cerebral hemisphere there was a 4 x 4 cm recent hemorrhage which extended from the Sylvian fissure posteriorly to the splen-

ium 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 ex-

ceeding 3.5 cm in length.

Microscopic examination showed that the walls of the cavity in the right parietal-occipital re-

gion contained numerous hemosiderin-laden macrophages-findings typical of an old hemor-

rhage. The perivascular spaces of many small blood vessels in the tegmental portion of brain-

stem 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. Micronodules were in-

creased around these vessels.

2 Cranial Nerve Disorders. Many abnor-

malities of cranial nerve function have been

described with SLE; however, these abnor-

malities may be brought about in several ways. They may be the result of lesions in cortico-

spinal tracts at a cerebral level, of intramed-

ullary lesions within the brainstem, of lesions

within the peripheral cranial nerves them-

selves, or of a disorder at the myoneural junc-

tion 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 patho-

logically (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. Papil-

ledema has been seen (16, 33, 66, 74, 84, 96, 107, 123, 142) with normal spinal fluid pressure

(58, 123, 154) and with increased pressure

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120, 216, 229) 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 de-

scending pathways (34, 104, 138, 202) clearly

demonstrating 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 hypopesthesia, 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 mellitus (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 1 transient diplopia during the last month of life were found; in Case 7 transient diplopia 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 fevers and arthritis. Seven months after the onset of the arthritis she developed severe left upper quadrant pain and was found to have massive spasmography and a white blood count of 420,000. 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 intern-
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 Fryse-Phillips and Yorkston (161) who developed a sudden hemiparesis eight years before the signs of SLE and a patient reported by Rudsky (172) who had transient hemiparesis and aphasia 32 years preceding signs of SLE. Seikert and Clark (188) reported hemiparesis preceding other manifestations of SLE by six months, and Silverstein (159) 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, 32, 68, 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, 33, 33, 49, 65, 66, 90a, 118, 132, 138, 157, 141, 133, 168, 180, 213). The recurrence of hemiparesis in Osler’s patient remains unique, although Sedgwick and Von Hagen (159) 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 Morrier (136, 137) with hemiparesis three and six years ante-mortem had multiple small lesions with occlusions of small arteries or arterioles. Two patients reported by Mintz and Fraga (122) 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 Hannahan (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 acuic 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, parasthesias, 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 15-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 visual 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 afibrile with a blood pressure of 100/70. A butterfly rash, mild hepatosplenomegaly, minimal effusions of both knees, albuminuria and positive E.E. phenomena 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. In- volvement was poor and left affect was inappropriate and euphoric; no delusions of hallucinations were detected. Examination of the cranial nerves and upper extremities showed no abnormalities. The lower abdinal 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 there was no sphincter control. A urinalysis disclosed no abnormalities. The lower extremities and perineum were 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 and strength continued to improve, and she became able to walk a few steps with assistance; the plantar reflexes became extensor. 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 122 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 nonsensical rhyming and punning. Over the next week she began having visual and auditory hallucinations and became intense paranoid, threatening and attacking ward personnel. Her constant speech was rhythmic and scanning in jambic meter, described as "reminiscence of James Joyce". An electroencephalogram and repeated spinal fluid examination were normal. Over the next three months cortisone was increased to 200 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
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, 52, 55, 53). 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 (3, 10, 90a, 103, 158, 204, 215); others have been reported with predominant or exclusive motor loss and elevated spinal fluid protein resulting in a Guillain-Barré syndrome (10, 15, 69, 76, 87, 112, 177, 180). 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 mononeuritis multiplex similar to the peripheri nerve involvement associated with polyarteritis. These reports have included eighth cervical or brachial root palsy (158), ulnar nerve palsy (64, 103), bilateral wrist drop (71), bilateral hypesthesia over lumbar dermatomes (158), bilateral sciatic nerve palsies (39), and peroneal nerve palsy (158). 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...
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 mid-calf. 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 arteries within nerves. In a patient who had been recovering for one year from a subacute polyneuropathy, Scheinberg (177) found vascular lesions in peripheral nerves but no axonal degeneration and amorphous fibrinoid material spreading the fibers. Similar amorphous fibrinoid material within peripheral nerves was found by Anderson (5) associated with Schwann cell degeneration. Fibrinoid degeneration of perivascular collagen and myelin loss. Less extensively pathological reports have been made by (88) who found polyneuritis in a case of "peripheral neuritis," and Contador Slim et al (39) who found no abnormalities in peripheral nerve of a patient with oral sciatic palsies although fibrinoid degeneration was present in the leptomeningeal vessels. In nerve biopsies from patients with cutaneous 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 Siguiet 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 dose 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 mid-calf. 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.

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vessels, verrucous endocarditis, wire loop lesions of kidneys, onion skin lesions of spleen, and focal necrosis of lymph nodes. The brain weighed 1300 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 postrema. 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 (132) described four patients with SLE who developed "cigarette rolling" tremor with rigidity resembling paralysis agitans. Poch (153) 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 cerebrovascular 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, 189). One patient's chorea occurred with pregnancy ("chorea gravidarum") and was reported to resolve following a therapeutic abortion (134); others have shown predominantly 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 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 "dying" 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 (153) 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-Efrain (100) reported a patient with hypothalamic 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 33-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 comatose, but neurological examination, lumbar puncture, and electroencephalogram were normal. One month later coincident with an exacerbation of fever and arthritis she suddenly developed severe hiccup and diplopia. A left abducens palsy and left extensor plantar response were found. On the following day, cortisone was started with prompt recovery. Within a week full abduction of the left eye returned, but nystagmus of the left eye on lateral gaze and the left Babinski sign 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, obliterator pericarditis, pleuritis, perirenal, 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 lerrugination 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 (50). The frequency of psychosis varies greatly in different series: in psychiatriconly oriented studies incidences of 2 percent by Brody (22), 52 percent by O'Conners (143), and 49 percent by Stern and Robbins (196) 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 reported.
ably frequent in SLE (7, 23, 33, 36, 58, 59, 72, 81, 90a, 125, 127, 136, 140, 142, 146, 149, 158, 163, 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 (61) 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). These patients had mild affective manifestations 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 up to death and two were transient. One patient (Case 6) had two transient episodes of paranoid delusions and another (Case 15) had a transient psychotic episode, which was associated with increased activity of disease during 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 flood 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 examination she had a generalized convulsion. She remained psychotic for the remaining six weeks of life converting to a mute catatonian 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...
NEUROLOGICAL MANIFESTATIONS OF S.L.E.

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, leukopenia, 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 extensor. 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 or 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 alexia, 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 convolution, 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 insipicence.

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 23 (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 800 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 10,000 cells (61) and a case with confusion and cogwheel rigidity has been reported with 800 cells (216). In both cases cells were predominantly polymorphonuclear cells, yet no evidence of meningitis was found at autopsy. In most cases marked pleocytoses have been predominantly lymphocytic (62, 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 (209) presented a similar case whose spinal fluid pressure was 270 mm without elevated protein or pleocytosis. Elevated pressure has also been reported by others (64, 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 slowing has been the most frequent finding. Spikes or sharp waves have rarely been reported (12, 13, 24, 26). Electroencephalograms were performed on patients in this series of whom seven had convulsions; in three cases they were recorded (including the patient without seizure three there was diffuse slowing, and in the remaining two there were bilateral paroxysms of 3/sec activity.

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

D. Effects of ACTH and Corticosteroids. Neurological Manifestations

The effects of ACTH and adrenal steroids on the neurological manifestations of SLE is difficult to determine because of the diversification of complications and their frequent transient nature. Coma (132), encephalopathy (206), increased intracranial pressure (208), cranial nerve disorders (100), hemiparesis (65, 66, 77), myelitis (77), neuropathy (5, 53, 97, 113), chorea (25, 53) have all been reported to have disappeared or improved subsequent to therapy. Dubois and Tuftanelli (57) reported recovery in three of five peripheral neuropathies on steroid therapy. However, the natural history of any of these disorders is characterized by spontaneous recovery so the relationship of recovery to treatment is tenuous. In the present series 15 patients received ACTH or cortisone, but in no instances this was only given during the 7 days or weeks of life. Of the ten instances of cranial nerve disorders seven evolved while patients were receiving treatment; in two development of signs was temporarily related to a discontinuation of ACTH, but in no instance was improvement clearly related to the institution of treatment. Furthermore, the effect of severe paraplegia and peripheral neuropathy was clearly deteriorated while on treatment, as in the case with an apparent hypothalamic hyperglycemia syndrome developed her symptoms two days beginning cortisone. Certainly, no efficacious adverse effect of steroids on these neurological 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. Soifer 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, Brunswick 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 (150, 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 6 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 an 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, 118, 125, 173, 192, 193, 194). The problem of causation arises with the development of affective or schizophrenic reactions. Soifer et al (193) noted a 63 percent incidence of euphoria, depression or paranoia in patients with SLE receiving long term cortisone or corticotropin. 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, 110, 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, 155, 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 schizophrenic disorders 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 (65) 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 Wai (210, 211) in Russia, but their primary interests were in changes in autonomic ganglia. They speculated that the symmetry of systemic lesions must be due to 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 1938; he found occluded small vessels with microinfarcts in a patient who had had no clinical neurological abnormalities. Since then small infaracts with small arterial or arteriolar occlusions have frequently been reported (6, 14, 18, 27, 37, 46, 58, 61, 72, 75, 90a, 114, 121, 123, 138, 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 infaracts 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 to emboli from verrucous endocarditis, and this explanation was supported by Adams and Michelsen (2). The only case in which emboli have been demonstrated in cerebral vessels was in a patient with verrucous endocarditis reported by Albertini and Alb (4); in that case there were also embolic lesions in the kidney, spleen, and coronary arteries. In most cases, however, embolic infarction is usually not found in other organs, and endocarditis occurs considerably less frequently than cerebral infarcts. Furthermore, in the present series there was no consistent relationship between cerebral lesions and endocarditis. Therefore, most cases cerebral lesions are not on an embolic basis; instead, cerebral microinfaracts and hemorrhages must be due to an intrinsic order of cerebral vessels. The exceedingly small size of most infarcts and the occurrence of pericapillary microglia proliferation suggest that the underlying pathological process in the brain vessels of the nervous system affects mainly small arterioles or capillaries. However, on reviewing the literature or studying the present cases a single or distinctive lesion of the vessel cannot be found. In both this study and previous reports there is evidence of inflammatory, destructive, and proliferative cerebral vascular changes (Table 5).

The assumption is often made that the lesion is inflammatory, yet true arteritis of cerebral vessels has been a rare finding (18, 35, 32, 132, 157, 177, 190). On the other hand, vascular infiltrates of inflammatory cells have frequently been noted (6, 14, 58, 61, 64, 72, 121, 124, 145, 150, 175, 195, 204, 213), but the significance is unknown. True vascular inflammatory cells within the vessel wall were found in only 3 of the 24 cases in this study, and in none of these cases was it a primary or generalized phenomenon. In Case 2 the inflammatory reaction was almost entirely vascular and localized to subependymal arteries. Adjacent to the intracerebral hemorrhage in that case there were occasional polymorphonuclear cells within vessel walls; these cells were more consistent with a secondary reaction to the intracerebral and subarachnoid hemorrhage than with primary vascular disease. Case 10 a few polymorphonuclear cells were found within the walls of both arterioles.
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### Table 5—Continued

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age and sex</th>
<th>Duration of disease in years</th>
<th>Interval between onset of neurological disease and death</th>
<th>Neurological findings</th>
<th>Greco</th>
<th>Microscopic</th>
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<tr>
<td>14</td>
<td>24F</td>
<td>1</td>
<td>6 wks.</td>
<td>Recurrent Jacksonian seizures, weakness in right leg, and right hyperreflexia (uremia)</td>
<td>Small infarct in left frontal lobe</td>
<td>0</td>
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<tr>
<td>15</td>
<td>34F</td>
<td>2</td>
<td>4 mo.</td>
<td>Schizophrenic reaction unassociated with treatment lasting 3 days (uremia)</td>
<td>None</td>
<td>0</td>
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<tr>
<td>16</td>
<td>23F</td>
<td>2</td>
<td>1 yr.</td>
<td>Single left-sided seizure (heart failure)</td>
<td>None</td>
<td>0</td>
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<tr>
<td>17</td>
<td>21F</td>
<td>0.3</td>
<td>1 day</td>
<td>Two seizures (uremia)</td>
<td>None</td>
<td>0</td>
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<tr>
<td>18</td>
<td>18F</td>
<td>2</td>
<td>1 day</td>
<td>Terminal seizure (pneumonia)</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>25F</td>
<td>0.2</td>
<td></td>
<td>None (pneumonia)</td>
<td>Recent small subpial hemorrhage</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>22F</td>
<td>0.6</td>
<td></td>
<td>None (pneumonia)</td>
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<td>0</td>
</tr>
<tr>
<td>21</td>
<td>33F</td>
<td>1</td>
<td></td>
<td>None (heart failure)</td>
<td>None</td>
<td>0</td>
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<tr>
<td>22</td>
<td>40F</td>
<td>1.5</td>
<td></td>
<td>None (uremia)</td>
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<td>0</td>
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<tr>
<td>23</td>
<td>23M</td>
<td>2</td>
<td></td>
<td>None (pneumonia)</td>
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<td>0</td>
</tr>
<tr>
<td>24</td>
<td>22F</td>
<td>5</td>
<td></td>
<td>None (constrictive pericarditis and pneumonia)</td>
<td>None</td>
<td>0</td>
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</table>

### Notes:

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 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, 26, 61, 72, 90a, 121, 126, 129, 145, 150, 157, 175) or as hyalinization and necrosis (6, 44, 66, 213). Destructive necrosis were found in cerebral vessels in five cases in this study. In each case there was necrosis of the vessel wall with extravasation of red blood cells and fibrin. In Cases 1, 10, and 13, all of whom died of acute CNS disease, this was a prominent finding (Fig. 2 and 3). Fibrin thrombi were also found occluding small vessels in each of these cases. In Case 13 there was a history of hypertension, and terminally there was a pontine hemorrhage. In this case the necrosis of small vessels was also found.
was not possible to actually quantify 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 brain 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. 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, X 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 retraction of the wall resembling fibrinoid degeneration.

Daly (40) first described proliferative changes in intima of cerebral vessels of less than 100 μm in diameter, and similar proliferation or swelling of cerebral endothelial cells has been noted by others (6, 10, 14, 18, 55, 72, 90a, 129, 133, 136, 145, 195, 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, 25, 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

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 cosin stain, X 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 hemorrhage in SLE was explained in one case reported by Harvey et al. (84) on the basis of rupture of “small aneurysm associated with lupus arteritis” but no similar observations have been made in others. Even in hypertension the pathogenesis of intracerebral hemorrhage is unknown. Rosenthal (169) has postulated that the intracerebral hemorrhage is not the result of elevated intravascular pressure or aneurysm formation, but rather that the small vessel disease accompanying hypertension leads to the hemorrhage. There is evidence that in SLE intracerebral hemorrhage appears to result from primary disease of arterioles and capillaries in the absence of blood pressure elevation tend to support this hypothesis.

Polyarteritis nodosa more frequently involves the peripheral nervous system but may involve the CNS in about 20 percent of cases (60, 131). In contrast to the vascular lesions in SLE, the lesions of polyarteritis are characterized by intense cellular inflammatory reaction within the vessel wall. Furthermore, polyarteritis involves predominantly medium-sized to small arteries whereas in SLE the smallest arteries, arterioles, and often capillaries are affected. There is little similarity of the cerebrovascular lesions in the
two diseases, yet in Case 11 typical polyarteritis
was found in the one medium-sized artery, and in
Case 1 typical polyarteritis lesions were found in
vessels (22), although not in cerebral vessels.
Thus, some overlap of pathological findings in
the vessels does exist.

- Brain purpura was also found in single case
(Case 9) in addition to cortical and brainstem
microinfarcts. The lesions of brain purpura are
characterized by a pericapillary focus of coagu-
larized antihuman globulin; no evidence of
brain purpura in a patient died of acute rheumatic fever, were described in the same paper.

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bivalization, and necrosis of small vessels and
pervascular infiltrates (195, 210). Again these are
findings that occur in some cases of SLE. Exam-
ination of the brains of rabbits with acute serum
sickness by one of us (J.T.T) showed no lesions re-
ssembling 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-la-
beled 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 pre-
seding 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 widely dis-
tinctive 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 inflamma-
tory 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 ves-
sels in SLE are not distinct from some of the
vascular changes found in hypertensive ence-
phalopathy, thrombotic thrombocytopenic pur-
pura, acute rheumatic fever, and serum sick-
ness. However, the neuropathological lesions of
SLE are characterized by their being more
focal or scattered than is usual with these dis-
cases and by the fact that they vary in age
from region to region, rather than appearing to
have occurred simultaneously in many lo-
calizations.

V. CLINICAL-PATHOLOGICAL CORRELATIONS

In general the clinical neurological manifesta-
tions 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 wide-
spread 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 10) 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 microinfaracts 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 palsy 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 pupillomotor 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 extensive search uncovered no lesions within vessels, so that some mechanism other than vascular occlusion must be considered in case.

In the patient with peripheral neuropathy (Case 5) a non-vascular cause of the neurological changes must also be considered. Although mononuclear cells were found at blood vessels within the peripheral nerves, there was no vasculitis and no vascular occlusion were found. Pathologically the findings in peripheral nerves bore more resemblance to those seen in idiopathic polyneuritis (Guillain-Barre syndrome) than to the vascular lesions found in polyarteritis. Clinically symmetry of the neuropathy also suggested diffuse disease of nerves rather than multiple mononeuropathies secondary to neural involvement. The reported clinical syndromes and pathological findings in neuropathies associated with SLE suggest two distinct disease processes. In some cases, mononeuropathies secondary to vascular disease are found (10, S3). In other a symmetrical neuropathy evolves with pathological findings suggesting a relationship to 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 for neuropathy in all cases.

One cannot help but wonder whether vascular disease alone can lead to the clinical disorders of mental function observed in SLE. At least some of these abnormalities must on a basis of observable pathological change. The acute confusional states and delirium probably result from widespread cerebral edema, and the frequent occurrence of hallucinations might suggest temporal lobe involvement. On the other hand, pathogenesis of the disease concepts are inadequate to explain the schizophrenic and affective reactions that occur in SLE. The reactions tend to occur during exacerbations of the disease and are often associated with other neurological abnormalities and in all cases of psychosis in this series disturbances related to small vessels were found. Nevertheless, whether or not these vascular changes are sufficient to account for the astounding abnormalities of mental function is uncertain. Recently in a patient dying durin
NEUROLOGICAL MANIFESTATIONS OF S.L.E.

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 rarely involves the peripheral nervous system (85% 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 probably 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 (32%, 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-Barré 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 nonspecific.

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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