MEDICAL PROGRESS

EPIDEMIC NEUROMYASTHENIA — CLINICAL SYNDROME?*

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DURING the past ten years an impressive number of outbreaks of bizarre, clinically similar illnesses have been reported from several areas of the world. The cases have shared the features of a protean symptomatology, including fatigue, headache, alterations in emotional status, aching muscular pain, paresis and paresthesias. Relative to the severity of the illnesses, few significant and consistent physical findings and abnormal laboratory determinations have been noted. The courses of the patients have been unaccountably prolonged and debilitating and marked by frequent exacerbations. Cases have been confined principally to young and middle-aged adults; females have been more frequently and severely afflicted. Although most of the outbreaks have involved the general community, the most notably susceptible have been nurses and physicians. Intensive efforts to characterize these illnesses, etiologically and pathologically, have met with little success.

The illnesses have been termed, variously, "Iceland disease,"[1] "benign myalgic encephalomyelitis,"[2] "Akureyri disease,"[3,4] "epidemic vegetative neuritis,"[5] "acute infective encephalomyelitis,"[6] "encephalomyelitis,"[7,8] "persistent myalgia following sore throat,"[9] "a disease resembling or simulating poliomyelitis,"[10,11] "atypical poliomyelitis,"[12] "encephalomyelitis resembling poliomyelitis"[13] and, more recently, "epidemic neuromyasthenia."[14,15]

Careful appraisal reveals differences among the various epidemics, but most of these concern minor details. The apparent similarity in the courses of illness, the common nature of most symptoms and signs, the remarkable paucity of abnormal laboratory determinations and the similar epidemiologic characteristics suggest a nosologic, if not etiologic, association among the various outbreaks. Reviewed are the epidemics that to us appear to share these basic associations. Included are data from epidemics presently recorded in the literature, reports of several of significance previously overlooked by others and a number of unpublished reports of epidemics obtained from sources as gratefully acknowledged.

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HISTORY

Attention was focused on this group of illnesses in 1950 by Sigurdsson and his associates,[10] who reported from Iceland an epidemic of over 1000 cases of an illness, superficially simulating poliomyelitis but presenting a number of inconsistent features. Among these were the following: a clinical course marked by easy fatigability, disturbances in sensibility and emotional instability persisting for several years[3]; an inordinately high community attack rate of 6.7 per cent; a morbidity rate twenty times higher among those fifteen to nineteen than those zero to four years of age; and an absence of deaths. Fecal specimens from acute cases injected intracerebrally into rhesus monkeys and by various routes into other laboratory animals, including suckling mice, proved negative. Serums were found negative by complement-fixation tests for the arthropod-borne encephalitides, choriomeningitis, rabies and Q fever, and by hemagglutination-inhibition tests for influenza viruses.

Reports of outbreaks of clinically similar but previously unrecognized illnesses followed in succeeding years from England, Australia, South Africa, Denmark, Germany, Greece and, in the United States, from Florida, New York, Maryland, Alaska, Connecticut and Massachusetts (Table 1).

Preceding the report of the outbreak in Iceland were 2 epidemics in the United States and 1 in England, all of which, in retrospect, bear it a striking resemblance. Gilliam[12] documents in detail an outbreak in 1934 of 198 cases among personnel at the Los Angeles County General Hospital during which 10 per cent of the 1531 physicians and nurses were afflicted. Occurring concomitantly in Los Angeles and in other areas of California were many cases that were considered typical of paralytic poliomyelitis and a great many others that were not.[24] In addition to a number of hitherto unknown clinical manifestations particularly among adults, epidemiologic appraisal of reported cases revealed an unusually high attack rate, a low paralytic and case fatality rate and a relative age selection for adults, particularly females.[17] Gilliam believed that the symptomatology among the hospital personnel was not characteristic and that the very high attack rate among the hospital personnel was without parallel in the history of poliomyelitis. He concluded, however, that since classic poliomyelitis prevailed among a large number of the patients with

Reprinted from the *New England Journal of Medicine*
260:757-764, 814-818 (April 9 & 16), 1959

communicable disease in the hospital, the simpler explanation of the facts was that the atypical disease seen among the hospital staff was the same.

Two years later, after studying an outbreak of 32 similar cases among 63 novitiates and candidates at a convent in Fond du Lac, Wisconsin, Armstrong[25] concluded that the disease "is not explainable on the basis of any infection or intoxication with which I am familiar."

Described by Houghton and Jones[9] were 7 cases occurring over a four-week period in the fall of 1939 among young nurses at Harefield Sanatorium in England. The illnesses began with an apparent streptococcal pharyngitis, but after seven to fourteen days, a multiplicity of debilitating symptoms developed, evolving into the clinical picture and course similar to that described elsewhere. The authors were unable to identify the illness and suggested tentatively that an unidentified virus might be the cause.

Epidemics of similar illnesses occurring between 1939 and 1948 are unknown to us. Since almost two thirds of the recorded outbreaks have occurred during or at the end of the usual poliomyelitis season, and since they present a number of clinical features in common with poliomyelitis, misidentification may have occurred. It would be surprising indeed if no outbreaks had occurred in view of the relative frequency of reports since 1948.

TABLE 1. *Apparent Outbreaks of Epidemic Neuromyasthenia.*

LOCATION	YEAR	NO. OF CASES REPORTED	NATURE OF OUTBREAK
United States — Los Angeles, California*	1934[12,16-24]	198†	Hospital staff; community.*
United States — Fond du Lac, Wisconsin	1936[25]	35	Convent candidates & novitiates
England — Harefield	1939[9]	7	Hospital staff
Iceland	1948-49[3,4,10]	1090	Community
Australia — Adelaide	1949-51[11,26]	800	Community
United States — Louisville, Kentucky	1950[27]	37	Student nurses
United States — Northern New York	1950[1]	19†	Community
Denmark	1952[5,28]	10†‡	Community
United States — Lakeland, Florida	1952[29]	27†	Community
England — London (Middlesex Hospital)	1952[30]	14	Student nurses
England — Coventry	1953[31]	13†	Hospital staff; community.
United States — Rockville, Maryland	1953[14]	50	Student nurses predominantly; community.§
United States — Tallahassee, Florida	1954[32]	450	Community
United States — Seward, Alaska	1954[33]	175	Community
Germany — Berlin	1955[34]	7	Barracks group
England — London (Royal Free Hospital)	1955[7,8,13,35,36]	300	Hospital staff; community.¶
South Africa — Durban	1955[37,38]	140†	Hospital staff; community.
United States — Ridgefield, Connecticut	1955-56[39]	70	Community
United States — Punta Gorda, Florida	1956[15,40]	124	Community
United States — Pittsfield — Williamstown, Massachusetts	1956[41]	7	Community
England — London (Royal Free Hospital)	1956[6]	7	Student nurses
England — Coventry	1956[42]	7	Community
Greece — Athens	1958[43]	27	Hospital staff

*198 cases at Los Angeles County Hospital documented in detail by Gilliam.[12] From other reports[16-24] large numbers of similar cases seen elsewhere in California.

†Number noted indicates only cases studied. Additional cases known or thought to have occurred.

‡10 cases reported in detail by Fog.[5] An additional 70 cases were reported but only sketchily described by Heidemann.[28]

§Community cases suspected.

¶Community cases described by Ramsay and O'Sullivan.[13]

CLINICAL CHARACTERISTICS

Features in common among cases in these outbreaks are headache and aching pains in the extremities and usually the neck and back, associated with symptoms of paresis in one or more muscle groups. Initial appraisal has suggested to most observers the diagnosis of poliomyelitis. Subsequently the protean symptomatology, accompanied by emotional instability and depression, a relative paucity of physical findings (and these often of a bizarre nature) and the lack of signifi-

cant laboratory findings has led to the consideration of psychoneurosis or mass hysteria as the underlying problem. Increasing numbers of remarkably similar cases sharing also the features of protracted debility and recrudescences over months to years have indicated to each investigator an illness foreign to his previous experience.

Although the clinical and epidemiologic descriptions indicate a close relation between epidemics, there are differences in the over-all severity of cases from one outbreak to another and well defined differences in presence or absence of some symptoms and physical findings. For a number of reasons, the differences may be more apparent than real; protean symptomatology makes complete recording of all findings difficult; physical findings are frequently on the borderline of abnormality and may be recorded or disregarded depending on the observer; patients were seen almost at the onset in some outbreaks whereas in others the evaluation was not begun until several weeks of illness had elapsed; and in some cases it is probable that an effort to make the clinical picture conform to some conventional neurologic process unwittingly biased observations. Because of these factors, construction of a comprehensive table that quantitatively compares the symptoms and physical findings among outbreaks is impossible. For purposes of orientation, however, a summary of the more prominent clinical features is presented in Figure 1. These, with other notable aspects of the illnesses, are discussed below in a narrative synthesis that seeks to embody the impressions of other writers and our own about the natural history of these illnesses.

Within each outbreak, there is a spectrum in the severity of illness. Apparently milder cases present some combination of the prodromal symptoms of fatigue, headache, diffuse, aching muscular pain, upper respiratory infection, diarrhea, tension or low-grade fever, most of the symptoms subsiding within a few days or weeks. Because of the uncertainties of diagnosis of such cases, authors, when compiling clinical and epidemiologic statistics, have commonly disregarded these illnesses. The clinical picture discussed relates then principally to the moderate or severe cases.

The onset of illness ranges from a fairly abrupt to a more usual, insidious evolvement of the prodromal symptoms already noted. This phase extends over a period of a few days to several weeks and may be difficult to date precisely. The symptoms may be intermittently or constantly present. A respiratory infection, often reported at the outset, may be accompanied by mild cough or coryza, tender lymphadenopathy most evident in the posterior cervical chain and, rarely, conjunctival injection or pneumonitis. Diarrhea, usually mild and of fairly brief duration, is frequently alluded to, particularly in the early course of the illness.

After a period of days to three or four weeks, there is often an abrupt exacerbation of symptoms accompanied by paresis, paresthesias, changes in emotional status and mentation, and dizziness, nausea or blurring of vision, with, in some patients, even vertigo, projectile vomiting and diplopia. This acute phase persists for one to several weeks and is accompanied by numerous symptoms, many of which are difficult to evaluate in the presence of tension, depression, anxiety and alterations in mentation.

Malaise and fatigability are particularly pronounced and persist long into convalescence. Headache and extremity, neck and back pain are usually present in about that order of frequency. The headache is commonly suboccipital or generalized although other variants are described. It is moderate to very severe in intensity, and usually nonthrobbing in character. The extremity pain is aching, diffuse, poorly localized and, in general, more frequent in the lower limbs, although in some outbreaks it appears to be more common around the shoulder girdle. Pain is usually present in more than one limb, not uncommonly is asymmetrical and may shift in location. The neck and back pain is of the same general character as that in the extremities. Nuchal pain and a sense of tightness in the nape of the neck or back on extreme forward flexion of the head are usual; nuchal rigidity is not common. Abdominal pain, initially mistaken for peritoneal irritation, has been found, on careful examination, to be related to the abdominal musculature. Pleuritic-type chest pain, occasionally associated with a friction rub, has been related by some observers not to pleural irritation but to lesions in the intercostal or diaphragmatic musculature.

Uniformly present in all outbreaks, although not in all cases, is paresis, which usually begins with the acute illness but may be delayed for a period of days to several weeks. Manifestations of paresis seem to be of two general types. Most common initially is a diffuse weakness of one or more limbs usually accompanied by aching pain and a sense of heaviness in the affected part. Some have commented on this form of paresis as appearing to be more a disinclination than an inability on the part of the patient to contract the muscles. Deep tendon reflexes in the affected extremity range from being moderately hyperactive to depressed but are rarely absent or unilaterally unequal. Weakness of a similar type in the shoulder or hip girdle, back, neck and abdominal musculature has been observed.

The second form of paresis involves single muscles or muscle groups, more commonly in the hand, arm, lower leg, hip or shoulder girdle, the facial muscles or the external rectus of the eye. Foot drop in a few patients has been mentioned in several epidemics. Although sometimes evident during the early acute phase, weakness in these muscles usually becomes manifest with resolution of the more extensive paresis noted above and appears, in a few cases, to constitute permanent residual damage. Contraction of paretic muscles is often jerky and associated with a coarse

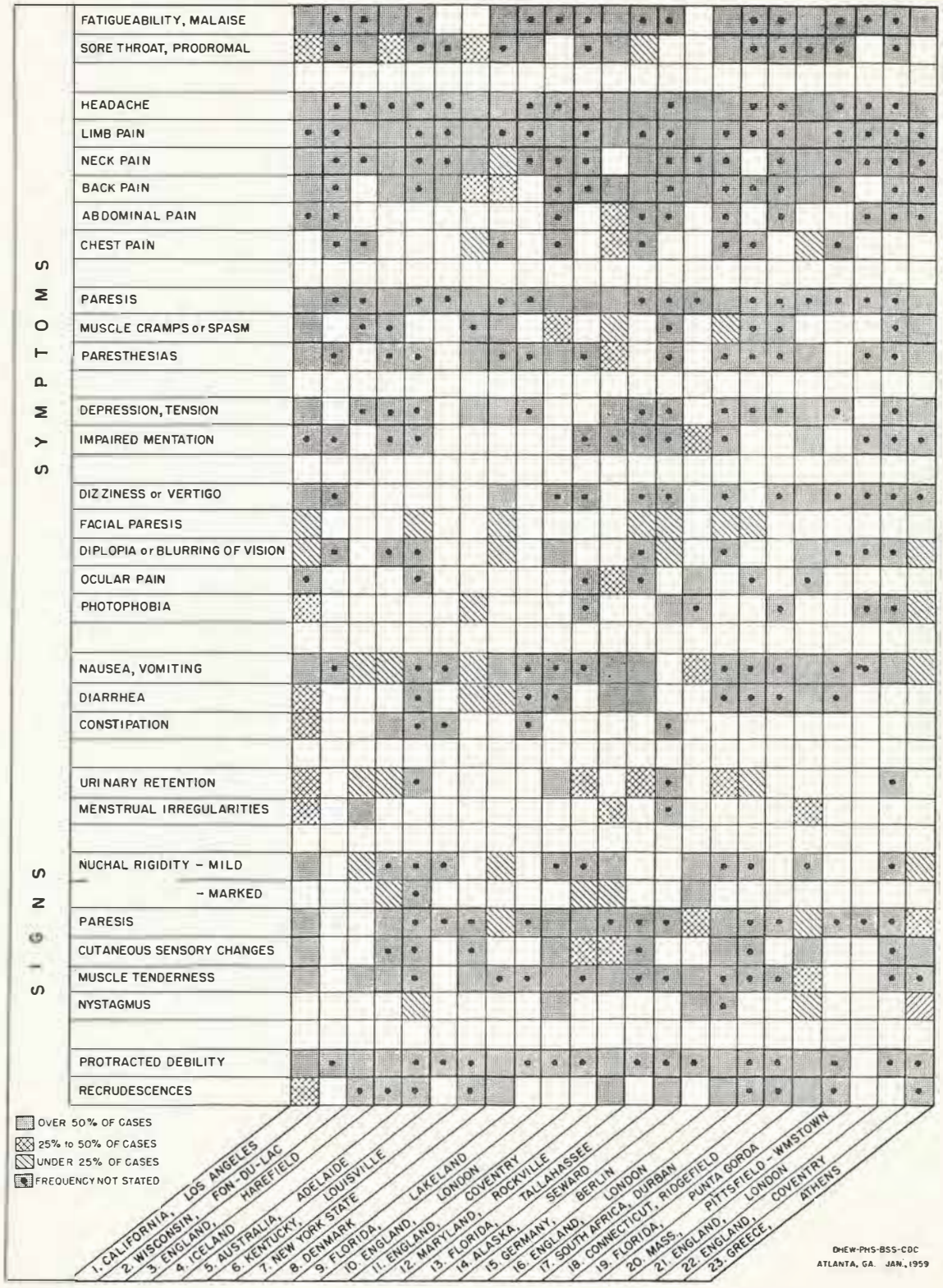

FIGURE 1. *Selected Symptoms and Signs in 23 Outbreaks of Epidemic Neuromyasthenia.*

tremor. Fibrillary twitching and painful myoclonic spasms of involved large-muscle groups are frequently described. Fasciculations are rarely present. Atrophy of the involved muscles is exceptional despite persistence of measurable paresis.

Involved muscles are commonly tender, either diffusely or in focal, discrete areas. Focal areas of tenderness are stable in location, and relieved sometimes by procaine injection but without evident improvement in strength of contraction of the involved muscle. More diffuse tenderness has been associated with muscles described as edematous, doughy or rubbery in consistence.

Present from early in the acute phase and often corresponding in distribution to the involved musculature are paresthesias, including numbness and tingling, hypesthesia or hyperesthesia and, occasionally, anesthesia. Severe hyperesthesia requiring the use of bed cradles has been observed. Characteristically, the paresthesias are shifting in distribution over a period of hours or days and do not usually correspond to a peripheral nerve or root distribution. Cutaneous sensory examination discloses a similar bizarre shifting pattern of areas of marked impairment of touch, pain and temperature or hyperesthesia to touch. Less commonly, cutaneous sensory changes correspond to peripheral nerve or root zones and may be associated with tenderness over nerve trunks, especially the ulnar or sciatic. Anesthesia is rarely observed. Loss of position and vibration sense usually in the lower extremities and corresponding to the distribution of muscular pain and paresis has been seen in a number of outbreaks. The Babinski sign was demonstrated in a very few patients in two of the outbreaks.

Depression, tension and emotional instability have been impressive and among the most incapacitating and persistent symptoms. Repeated episodes of crying without provocation, insomnia, terrifying dreams and difficulty in concentration are probably secondary phenomena. Persons tending to be emotionally labile before illness have appeared to be most severely afflicted.

Mild confusion, impaired memory for recent events, alterations in personality structure, euphoric behavior and tendencies to transpose and "stumble over" words have frequently been observed during the more severe acute phase and during recrudescences, although sometimes persisting into convalescence.

Common also as an initial symptom in the acute phase is "dizziness," which varies in severity from a commonly observed postural giddiness to actual vertigo among fewer cases. Nystagmus on lateral or upward gaze is found accompanying some of the severe illnesses, but, as with numerous other signs, seems to appear and disappear over the course of hours to several days. Persistent vomiting, sometimes projectile in character, commonly accompanies the vertigo. Vertigo rarely persists for more than a few days, but a postural "dizziness" may persist for many weeks or months. Other symptoms much less common but probably related to eighth-cranial-nerve involvement include tinnitus, hyperacusis and, uncommonly, transient hearing impairment.

Possible involvement of other cranial nerves is suggested by occasional transient facial pareses and the more regularly noted symptoms of blurring of vision or diplopia. These visual symptoms have often been associated with eye pain aggravated by movement, less commonly with photophobia. Most observers have been unable to demonstrate associated ocular-muscle weakness, although paresis of the external rectus with evident strabismus has been seen in some outbreaks. Symptoms of functional impairment of swallowing are not uncommon, but are only occasionally associated with palatal paralysis or regurgitation. Whether this symptom is related to cranial-nerve involvement, some lesion in the deglutitional muscles or emotional factors is not clear. During several outbreaks a few patients were placed in respirators, never for more than a few days. Clear documentation of respiratory embarrassment because of diaphragmatic or bulbar involvement, however, is not reported.

Gastrointestinal disturbances, particularly nausea, are common in the acute phase. These may or may not be related to vertigo. Diarrhea is usual early in the course, and constipation later.

A mild hepatomegaly without splenomegaly in somewhat less than a tenth of the patients was found in the Royal Free Hospital outbreak, but only 1 patient had evidence of jaundice.

Present inconstantly and in small numbers from epidemic to epidemic were symptoms of urinary retention without dysuria but of sufficient severity to require catheterization and occasionally tidal drainage. These symptoms subsided within five to six days.

Symptoms suggesting angiospasm have been particularly prominent in several outbreaks and rare or unremarkable in others. Hyperhidrosis, marked pallor and flushing or occasionally cyanosis of the hands or feet, accompanied by numbness and tingling over the affected area and sometimes edema, has been noted in several epidemics. These were so impressive in the Danish outbreak as to suggest primary involvement of the autonomic nervous system.[5]

Menstrual disturbances, including amenorrhea, menorrhagia and disturbances of cycle, have been repeatedly noted.

Throughout most of the illness, the temperature does not exceed 100°F. Early in the course a temperature of 100 to 103°F. occurs in a fourth to a half of the patients, but rarely persists for more than two or three days. Among three groups of carefully studied patients, an instability of body temperature was noted consisting of a variation of two or three degrees over the course of a day but within the normal range. As symptoms subsided, a more normal diurnal temperature fluctuation was assumed.

Course of Illness

After an acute phase lasting a few days to several weeks, there is a slow resolution of symptoms punctuated by exacerbations during which all the symptoms initially present may recur in their original, severe form and persist for days to weeks. Exacerbations commonly coincide with increased exertion, with cold or damp weather, in the premenstrual period, with trauma or with upper respiratory infection. The most persistent and incapacitating symptoms are fatigability and malaise, headache, neck, back and extremity pain, paresis, depression, irritability, impairment of concentration and paresthesias.

The protracted debility engendered by the illness is illustrated by studies from several epidemics. Among 198 cases in the Los Angeles County Hospital outbreak, the average time lost from work was fourteen weeks: 24 per cent of the personnel lost more than twenty weeks.[12] Inpatient hospital care among 300 cases from the Royal Free Hospital outbreak extended for periods in excess of a month in 43 per cent.[8]

In the sixth month after onset, studies of 21 patients from the Punta Gorda, Florida, epidemic revealed that 5 of the group were confined to bed for one or more days, and definite restriction of activity because of residual symptoms represented 43 per cent of patient days in that month.[15]

A few long-term follow-up studies have been carried out that suggest definite gradual improvement extending over several years' time. Exacerbations or relapses of varying severity, although mimicking the original acute phase of illness, became increasingly milder and of shorter duration.

Re-examination of 8 patients in New York State fifteen months after onset showed none to be completely without symptoms although the symptoms were mild.[1] Muscle pain, easy fatigability and more labile emotional habitus were the principal complaints. An eighteen-month re-examination of patients from the Punta Gorda outbreak revealed all to be much improved or essentially well.[40] Residual symptoms similar to those reported by the New York State patients were noted by some but were so equivocal as to be difficult to ascribe to the original illness.

A six-year follow-up study of 39 cases from the Icelandic epidemic, one of apparently greater initial severity than that in Punta Gorda, revealed that all patients had returned to work, but only 13 per cent considered themselves free of symptoms.[3]

Laboratory

White-cell counts have been reported as normal in most outbreaks, although ranging in a few patients as high as 14,000. In one series an absolute neutropenia was noted, 4 of 7 patients having total counts below 3000.[42] A relative lymphocytosis (counts of 50 to 60 per cent) during the acute illness was observed in the Maryland outbreak[14]; a low normal neutrophil count and a high normal lymphocyte count were found among half of 138 studied at the Royal Free Hospital.[8] In this outbreak abnormal adult lymphocytes, with cytoplasmic vacuolation, and plasma-cell-like forms, with coarsely reticulated nuclei and deeply basophilic cytoplasm, were frequently noted. The cells were not, however, considered to be those seen in infectious mononucleosis.

Erythrocyte sedimentation rates, when recorded, were rarely elevated. The exceptions were among patients from the Alaska outbreak, two thirds of whom were said to have had higher than normal values[33] and among nurses in the 1939 English outbreak, in which slight elevations were recorded.[9]

With few exceptions, cerebrospinal-fluid examinations have shown slight or no abnormality. In Table 2 are the compiled results from the reports in which the number of lumbar punctures performed is stated. A few cases in each of five outbreaks have shown pleocytosis between the time of onset and the twelfth day. Increased cerebrospinal-fluid protein was found in about the same number although not always in the same patients. Glucose and chloride determinations were normal. Colloidal-benzoin and colloidal-gold determinations in the Los Angeles outbreak showed a mid-zonal elevation in 18 of 59 cases.[12] Since these epidemics have tended to occur during or at the end of the enterovirus season and have sometimes been coincident with epidemics of poliomyelitis, it is conceivable that those with cerebrospinal-fluid abnormalities in fact represent cases of poliomyelitis, Coxsackie virus or ECHO meningitis. Conversely, because it is uncommon to see patients early in the course of the illness, transient cerebrospinal-fluid changes could be missed in the majority of cases. Interpretation of these data is thus difficult.

Liver-function studies performed in significant numbers in the Maryland[14] and Royal Free Hospital[8] outbreaks revealed but 1 to be notably abnormal in a patient from the latter outbreak who became clinically jaundiced.

Serial twenty-four-hour urinary creatine determinations performed on 10 adult patients from the New York State outbreak revealed initial levels in excess of 100 mg. daily among 9 of the 10, 6 of these returning to normal levels within four to seven weeks. Three patients showed little change during this period; 1 showed an increase from about 230 mg. to 300 mg. per 100 ml. at four weeks and to 400 mg. per 100 ml. at seven weeks.[1] Estimations of the serum cholinesterase in 7 patients and cerebrospinal-fluid cholinesterase in 1 patient were normal. Electrophoretic patterns showed no abnormality in these serums.[8]

Heterophil-antibody determinations in several outbreaks revealed no significant elevation except for 1 of 7 patients in the Coventry outbreak[42] and 4 of 121 in the Royal Free Hospital outbreak.[8] Repeat

determinations in the latter outbreak revealed, however, no change in titers — findings interpreted as indicative only of probable past infection.

Complement-fixation, neutralization and agglutination studies have been wholly unrevealing. Tests for antibodies for the following were reported negative in the various outbreaks: poliomyelitis[1,14,15,26,29,31-33]; lymphocytic choriomeningitis[10,15,26,29-32]; encephalomyocarditis[8,26,31]; Eastern equine encephalitis[10,15,29,32]; Western equine encephalitis[10,15,29,32]; St. Louis encephalitis[10,15,29,32]; Japanese B encephalitis[10]; Port Augusta encephalitis[26]; influenza[8,10,29,33]; Q fever[8,10,29]; leptospirosis[8,9,15,26,29-31,34]; trichinosis[9,14]; toxoplasmosis[8,15]; adenovirus[8]; herpes simplex[8]; psittacosis lymphogranuloma venereum[8,32]; brucellosis[8,9,25]; tularemia[25]; rabies[10]; typhoid[9,25]; paratyphoid[25]; louping ill[8]; Coxsackie A and B viruses[14]; ECHO virus, Type 6[14]; and *Salmonella typhimurium*.[14] A very few serums with elevated complement-fixation titers for mumps have been observed, but the majority have been negative.[8,15,26,29-32] Tests for cold agglutinins[34] and Wassermann reactions have been negative.[8,9,14] Toxicologic studies carried out in three outbreaks were unrevealing.[14,15,38]

Electroencephalography was performed on 19 patients from five outbreaks.[5,13,15,42,43] Borderline abnormalities of a nonspecific nature were seen in some, but all except 1 were interpreted as being within normal limits. One severely afflicted patient from the epidemic in Greece had a tracing showing paroxysmal or continuous slow-wave activity at high potentials predominating over the frontal leads and sometimes extending simultaneously to all leads.[43] Electrocardiograms obtained on patients in the Maryland[14] and Punta Gorda, Florida,[15] outbreaks were interpreted as normal. Three of 42 in the Royal Free Hospital epidemic showed abnormalities consisting of abnormal T waves in two or more leads and a prolongation of the QT interval in one. Two reverted to normal records. One patient with extensive neurologic abnormalities initially showed isoelectric T waves in Lead 1 and inverted T waves in Lead V_3 that, although improved over an eighteen-month period, were still abnormal at that time.[8]

Electromyographic studies have given conflicting results. Two Danish cases studied four months after onset showed neurogenic paresis of radicular or peripheral origin in isolated, involved muscle groups.[5] Observations in 20 cases from the Durban, South Africa, outbreak showed no abnormalities.[38] Among the 1953 Coventry cases, 3 during the fourth to eighth week of illness gave inconclusive evidence of partial denervation of muscle groups.[31] The most consistent evidence of dysfunction was reported among 28 cases studied from the Royal Free Hospital epidemic. Examinations carried out one or two months

TABLE 2. *Results of Cerebrospinal-Fluid Examination — 17 Outbreaks.*

LOCATION OF OUTBREAK	NO. OF PERSONS EXAMINED	NO. OF PERSONS WITH PLEOCYTOSIS*	NO. OF CELLS	DAY OF ILLNESS	NO. OF PATIENTS WITH ELEVATED PROTEIN	PROTEIN CONCENTRATION
			per cu. mm.			*mg./100 ml.*
California[12]	59	3	12,50,66	0,2,4	18	(12†; 6.‡)
Wisconsin[25]	2	0				
England[9]	1	0				
Iceland[3,4,10]	8	5	10,18,35 50,80	3,6,4 3,10	4	50,59,75,80
Australia[11]	59	5	44-88	7	2	45.60
Kentucky[27]	3	0				
New York[1]	11	2	27,44	4,12		
Denmark[5]	5	0				
London, England[30]	6	0				
Coventry, England[31]	9	0				
Maryland[14]	25	0			1	48,58,61
Tallahassee, Florida[32]	101	7	"Up to 15"	7		
Germany[34]	7	0			1	85
London, England[8]	18	0				
Punta Gorda, Florida[15]	5	0				
Coventry, England[42]	7	0			3	50,60,80
Greece[43]	4	0			1	66

*>6 cells/cu. mm.
†Trace of globulin.
‡+ test for globulin.

after onset showed largely unremarkable nerve-muscle excitability and nerve-conduction measurements, but electromyography, in the early stages, indicated some irregularly occurring fasciculation potentials of normal motor-unit-potential form. With the onset of paresis, a severe reduction in the number of motor-unit potentials on volitional movement of the affected muscles was apparent, of long duration and polyphasic in some cases. In the less severely involved and, particularly during recovery, the motor-unit potentials were grouped resulting in a tremulous contraction of 5-10 per second that rapidly fatigued. This combination of findings was thought to suggest a myelopathic lesion indicating involvement of the motor unit at the level of the spinal cord. The absence of lower-motor-neuron degeneration in the face of persistence of these lesions could not be explained.[8] Similar myographic findings were reported among 7 patients in the 1956 Coventry outbreak,[42] and 4 of 6 in the 1958 outbreak in Greece.[43]

Viral and Bacteriologic Studies

The nature of these illnesses has suggested to most a viral etiology, but, despite intensive efforts to implicate such an agent, results have been meager. Cerebrospinal fluid, feces, throat washings, acute-phase serums and blood clots have been inoculated by a variety of routes into many different laboratory animals and various tissue-culture systems. Despite the frequent use of blind passages, attempts to infect the following animals have thus far proved futile: suckling[1,8,10,14,15,26,29-31,34] and adult mice[8,14,26,29,31]; guinea pigs with[8] and without cortisone[10,26,31]; hamsters[8,10,14,26]; rabbits[26,31]; rats with and without cortisone[15]; ferrets[8]; and cynomologus and rhesus monkeys with[8,27] and without cortisone.[1,8,10,14,27,30,31] Embryonated hens' eggs of various ages injected into the chorioallantoic membrane, allantoic sack, yolk sack and amnion have yielded negative results.[8,14,26,27,29] Tissue-culture systems employed with similarly negative results include the following: monkey testicle[14,30,31]; monkey kidney[8,14,15,30,31]; HeLa cells[8,14,15]; human-embryo skin,[31] brain,[8] liver[8,15] and spleen[8]; human-infant kidney[8]; human fibroblast[14]; and human chorioamnion.[8,14]

Positive findings of possible significance are reported by Pellew and Miles[26] from specimens obtained from Australian patients. In their studies throat washings, feces and cerebrospinal fluid from each of 5 patients with acute cases were inoculated in combinations into paired young rhesus monkeys intranasally, and subcutaneously on three successive days. The monkeys inoculated with material from 2 of the 5 gave evidence of illness. One of the 4 had a lowered temperature (95°F.) on the eighth day and was sluggish. No definite abnormalities were found at post-mortem examination. The remaining monkeys showed sluggishness and abnormal temperatures between the sixteenth and eighteenth days. One showed wasting, particularly of the hind limbs and tremulousness and was killed on the eighteenth day. Of the remaining 2, 1 died on the twenty-seventh day, and the other recovered by the twenty-sixth day and remained well.

At post-mortem examination, the only gross abnormality was the occurrence of minute red spots along the course of the sciatic nerve in the last 2 monkeys. Microscopical sections showed localized infiltrations of inflammatory cells and exudation of red cells in the sciatic nerves. In the nerve roots close to their point of exit from the spinal canal there was pronounced infiltration with lymphocytes and mononuclear cells. In some of the nerve fibers axon swelling and vacuoles in the myelin sheaths were found. No abnormalities in the brain or spinal cord were detected. The heart muscle of the monkey that died showed severe myocarditis, with widespread infiltration of lymphocytes and mononuclear cells. Passage of a pool of brain, spinal cord, nerve, skeletal and heart muscle from these animals led to no illness in the monkeys inoculated. Repeat inoculation with the original material caused similar symptoms in 2 of 4 monkeys, but passage was again unsuccessful.[26]

Confirmation of these observations has not been forthcoming from other outbreaks.

Because of at least superficial resemblance of these illnesses to poliomyelitis, efforts to isolate a possible etiologic agent have been focused on viral studies. Thorough bacteriologic studies have been reported from the Maryland outbreak only.[14] Results obtained suggest at least a coincidental relation between cases of the disease, isolation from the stool of organisms of the Bethesda–Ballerup paracolon group and rises in serologic titer.

A total of 218 fresh fecal specimens from 113 persons, both ill and well, were painstakingly examined. Specimens were placed in enrichment mediums and then grown aerobically and anaerobically on a variety of selective and nonselective mediums. Obtained were 13 isolates of 2 strains of Bethesda–Ballerup paracolon organisms and 2 isolates of *S. typhimurium*. Serial serum samples from persons from whom the latter organisms were isolated showed no antigen agglutination with these organisms, thus discounting their pathogenic significance.

Isolates of the Bethesda–Ballerup bacilli were obtained only from 12 nurses with the illness and an asymptomatic kitchen helper. One type (antigenic formula, 1a, 1b, 1c: 8, 9) was found in the stools of 7 nurses; the second type (formula, 2a, 1b: [21] 25, 26) was detected in the stools of 5 nurses; both types were isolated from a kitchen helper. Neither of the strains appeared in large numbers in the stools, and neither was isolated from more than two stools of the series obtained from any person.

H and O agglutinins for the freshly isolated strains were found in titers of 1:40 or greater in the serums of 15 of the 26 paretic patients, in 7 of the 24 with

"minor illness," in 3 of 27 nurses without illness and in the kitchen helper. Among 11 of the 22 ill nurses showing the presence of agglutinins, there was a rise *and* fall of antibody titers; in 5, there was a demonstrable rise, and in 3, a fall in the antibody levels (in the remaining 3, single specimens only were available).

Serial serum specimens from 9 patients from the Punta Gorda, Florida, epidemic tested against the two Bethesda–Ballerup strains from the Maryland outbreak showed 1 with falling O agglutinins and a 1:160 H agglutination titer that was preceded and succeeded by negative titers in other specimens.[15]

TABLE 3. *Age-Specific Attack Rates in Two Community-Wide Outbreaks.*

AGE	RATE IN AKUREYRI, ICELAND		RATE IN PUNTA GORDA, FLORIDA	
	MALE PATIENTS	FEMALE PATIENTS	MALE PATIENTS (WHITE)	FEMALE PATIENTS (WHITE)
yr.	%	%	%	%
0-9	1.4	2.0	—	—
10-19	11.7	13.2	10.9	10.7
20-49	4.8	11.1	9.1	11.5
50 & over	2.1	2.9	2.0	8.3
Average	5.1	8.3	4.7	8.3

EPIDEMIOLOGY

The epidemiologic features of these illnesses have been uniquely distinctive, and because of the absence of specific pathognomonic findings in the individual case, these features must be regarded as integral to the diagnosis. They include, particularly, the concentration of cases among young and middle-aged adults, the increased frequency and severity of cases among females, the virtual absence of illness among preadolescents and the marked susceptibility of nursing personnel and physicians.

Two epidemics in communities of similar size (Table 3) in which detailed data regarding age-specific attack rates were obtained include the outbreaks in Akureyri, Iceland[10] (population, 6887) and Punta Gorda, Florida[15] (population, 2020). The similarity in attack rates between these two outbreaks is notable. Most heavily afflicted were those between ten and forty-nine years of age. In the Akureyri epidemic, those aged fifteen to nineteen seemed particularly susceptible; in Punta Gorda, it was the group aged thirty to thirty-five. Although the rates indicate a predominance of female to male cases in the ratio of more than 1.5:1, the severity of cases among females in both epidemics was considerably greater. An absence or virtual absence of cases in persons under the age of ten is surprising, and despite intensive search for some minor illness variant among this group in Punta Gorda, none was found. Equally interesting is the decrease in freqency of cases beyond the age of fifty. In the Tallahassee outbreak, a similar age distribution of cases was noted, those aged twenty-five to forty-four being most susceptible.[32] All the other outbreaks have involved primarily young and middle-aged adults, principally females.

Suggestive that the disease may be one with which communities have had no previous experience or, at least, to which they have built up no immunity is the remarkable similarity in attack rates in different community epidemics (Table 4). The rates in the Seward, Akureyri and Punta Gorda outbreaks are essentially identical. That in Tallahassee is lower but may be the result of a less homogeneous spread of illness throughout this much larger community. In Table 4, the rates noted for Punta Gorda and Tallahassee are for the white population since Negro rates were somewhat lower in the former and over sixtyfold lower in the latter epidemic despite intensive search in both for cases among Negroes.

The differences noted between the larger and smaller community outbreaks suggest, and other studies support, the necessity of close contact for spread of the disease. With the exception of the outbreaks in Iceland[10] adjacent communities have not become involved, and a spread of illness to surrounding rural areas has been quite uncommon for all outbreaks, including those in Iceland. Outbreaks among groups in intimate contact (Table 5), particularly those living together in dormitories, have produced attack rates considerably in excess of those seen among comparable age groups in community epidemics. A tendency for aggregation of cases by households has been observed in several outbreaks.[10,15,18,32]

TABLE 4. *Attack Rates in Community Epidemics.*

LOCATION OF OUTBREAK	POPULATION	NUMBER ILL	PERCENTAGE ILL
Akureyri, Iceland[10]	6,887	465	6.7
Seward, Alaska[33]	3,000	175	5.8
Punta Gorda, Florida[15]	1,604*	104*	6.5
Tallahassee, Florida[32]	23,708*	346*	1.5

*White population only.

Disproportionate among the total of outbreaks is the number among hospital groups. Ten[6,7,9,12,14,27,30,31,38,43] of twenty-three epidemics studied dealt principally with cases among hospital personnel, although it is known or believed that cases in the surrounding community were occurring concomitantly in six of these.[7,9,12,14,31,38] Two outbreaks in which studies were principally of community cases, disclosed rates four or five times greater among medical and allied personnel[15,32] than among similar age groups in the general community. Among 275 employees at the

Tallahassee Memorial Hospital, 16 cases were reported — an attack rate of 5.8 per cent as contrasted to 1.5 per cent for the white population of Tallahassee fifteen years of age or older. In Punta Gorda, medical and allied personnel had an attack rate of 42 per cent as compared to one of 8.6 per cent for white persons in the community aged ten to sixty-nine. That degree of exposure was probably the principal cause of these differences is further suggested by the virtual absence of cases at the university in Tallahassee, where a large student population of a presumably highly susceptible age resided.

TABLE 5. *Attack Rates among Groups in Close Association.*

GROUP	POPULATION	NUMBER ILL	PERCENTAGE ILL
Los Angeles student nurses[12]	401	65	16
Wisconsin convent[25]	65	32	49
Akureyri high-school residents[10]	70	34	49
Kentucky student nurses[27]	161	37	22
Maryland student nurses[14]:			
Paretic cases	66	19	29
All cases	66	36	55
Royal Free Nurses Preliminary Training School[7] — 1955	40	8	20
Royal Free Nurses Preliminary Training School[6] — 1956	27	5	19

Among those afflicted in major hospital epidemics, the nursing staff and physicians have shown particular susceptibility as contrasted with other hospital personnel. In the Los Angeles County Hospital epidemic[12] three groups within the hospital were delineated: occupations having intimate patient contact; occupations having less regular patient contact; and occupations rarely involving patient contact. Rates for these groups were, respectively, 8.2 per cent (169 cases among 2072 employees), 1.7 per cent (16 cases among 951) and 0.8 per cent (11 cases among 1291). These differences could not be accounted for by age differences between groups. In the Royal Free Hospital[7] outbreak, the rates among nurses, resident domestics, doctors and inpatients and ancillary medical, technical and social workers ranged from 13 to 18.6 per cent whereas among 2060 other employees, the rate was 2.2 per cent.

Analysis of cases among nurses by place of work in the Los Angeles epidemic[12] demonstrated that cases occurred considerably earlier and four times more frequently among those working on the communicable-disease wards and in the main admitting office than among those working elsewhere in the hospital. Further demonstration of the importance of intimate contact is obtained by a comparison of rates between personnel resident at the hospital contrasted to personnel not living on the hospital grounds. Among those resident at the Royal Free Hospital,[7] males experienced an attack rate of 20 per cent, and females one of 19 per cent; among nonresidents, males had a rate of 2.5 per cent, and females one of 6.1 per cent. Among residents at the Los Angeles County Hospital,[12] 9.4 per cent of physicians and 19 per cent of the nurses were afflicted whereas among nonresidents, only 3.1 per cent of physicians and 5.8 per cent of nurses were ill.

Although transmission of the disease to hospital inpatients has been noted,[7,12] the frequency with which this occurs is not known.

The relative restriction of outbreaks by communities or groups in close association has suggested possible common-source exposure to water, foods or some toxic agent in the environment. Efforts to identify such exposure have been made in several studies, but without success.[10,14,15,32] Additional evidence weighing against a common exposure, at least in community outbreaks, is the very high attack rate accompanied by the uniformly consistent selection of cases by age and sex and the noted predominance of cases among medical and allied personnel. It is difficult to postulate a chemical agent that would produce such an epidemiologic pattern.

The incubation time has been found to be between five and eight days when precise single dates of exposure could be determined.[7,10,12,14,31] Indirect determinations based on patterns of spread of illness and cases with continuing exposure suggest that the incubation period may be longer in some cases, but definite evidence of this is lacking.

Geography and Season

The epidemics are scattered in both latitude and longitude although concentrations are to be noted in the London–Coventry area of England and in Florida. This may reflect better recognition and reporting in these areas or may indicate a tendency for illness to recur in areas in which it is once established. With four exceptions, reported epidemics have been located on or very near salt water. Specific inquiry, however, during two epidemics regarding possibly related factors has been unrevealing.[15,32]

Over half the epidemics have occurred during the summer and particularly during the fall months, often succeeding or overlapping the latter portion of the poliomyelitis season in the particular area. This seasonal predilection accounts in part for the initial confusion in diagnosis between cases of these illnesses and poliomyelitis. The seasonal occurrence is not constant, however. Other epidemics are described that began in the fall and extended through the winter,[17] or appeared in late winter and continued through the spring,[15] in addition to other variants.

The Process, the Name and the Future

Crucial to a definitive classification and understanding of the group of diseases reviewed is a knowledge of the pathophysiology involved. Of this, essentially nothing is known. Deaths that occurred among definite cases during the acute phase or could be directly attributable to the illness have nowhere been reported. Two fatal cases occurring within a year of onset of illness have been noted, both of which occurred months after the initial episode and from unrelated causes. Post-mortem findings were wholly unrevealing.[8] Material for histologic study has almost been nil. The only positive finding reported is a nonspecific reactive hyperplasia found in a biopsied lymph node two weeks after the onset of illness in 1 case.[8]

The symptoms indicate a multiorgan system involvement, but which systems are primarily and which secondarily involved is not clear. There is agreement among investigators that altered functions in either the central or the peripheral nervous system or both must be present to account for many of the symptoms and findings, but confirmation through histologic study is lacking. To define the anatomic sites of lesions on the basis of symptomatology and physical findings is not as yet possible. A multifocal, changing process is postulated. If it involves the central nervous system, it does so in such a way that it rarely, or but briefly, alters the cerebrospinal fluid. Postulates based on these criteria have little precedent from other communicable diseases. A primary myalgic process has been considered likely by most investigators, but no histologic material to confirm this is available and electromyography to date has been confusing.

Etiologically, the Australian studies[26] indicate the possibility of a viral agent, and the Maryland studies[14] implicate a bacterial agent of the Bethesda–Ballerup paracolon group possibly as a toxin-producing pathogen, or perhaps as a fellow traveler with an unknown virus. These represent, as yet, but interesting leads.

In summary, despite intensive study by competent investigators in a number of different areas, the etiology and pathophysiology of these illnesses remains almost a total mystery.

As a group, however, the illnesses share a great number of common features and, both clinically and epidemiologically, present a unique and distinctive appearance. A nosologic relation is strongly suggested. For convenience of reference and identification a single descriptive name would be useful. Originally proposed by White and Burtch,[1] the name "Iceland disease" has been most commonly used in this country. Since this designation, however, has not been used in other countries, and since Sigurdsson, who originally focused attention on these illnesses through his studies in Iceland, objects to it, it seems wise to discard it. Sigurdsson in a counterproposal has suggested "Akureyri disease,"[3] named for the medical district in which the studies of his group were concentrated. To date, this has been ignored. In 1956 an editorial in the *Lancet* introduced the term "benign myalgic encephalomyelitis."[2] To those who have observed cases, the illnesses are anything but benign, except in terms of mortality. Encephalomyelitis, additionally, implies knowledge of a central-nervous-system inflammatory process of which there is presently no proof. English studies published since this proposal, with one exception,[42] have ignored this name. In reporting the Danish outbreak, Fog,[5] unaware of similar outbreaks, designated the illness seen in Denmark as "epidemic vegetative neuritis" because of what appeared to him to be major, although not exclusive, involvement of the autonomic nervous system. Objection must be registered to use of this term as well as to that in a recent English report, "acute infective encephalomyelitis,"[6] since both again imply knowledge of an inflammatory process that has not as yet been demonstrated. The latter term, in addition, properly includes essentially all the infectious encephalomyelitides, the etiology of many of which is well established.

To date, there is no agreement on a name, almost every epidemic receiving a different designation. For purposes of referencing and indexing, this presents a chaotic problem. Until an etiologic agent or agents are identified or until the underlying pathophysiologic processes are defined, we recommend use of the name, "epidemic neuromyasthenia."[14,15] This, we believe, meets previous objections and is specifically distinctive within the limits of current knowledge. Use of the word "epidemic" emphasizes the need for epidemiologic as well as clinical appraisal of cases. Diagnosis of a single, sporadic case of illness marked by a protean symptomatology without pathognomonic physical or laboratory findings and presenting many of the features of psychoneurotic illness is fraught with difficulty. Adequately characterizing the most prominent symptoms of the illnesses without reference to the underlying pathologic processes are the terms "neurasthenia" and "myasthenia" or, when linked, "neuromyasthenia."

In the light of the frequency of reports in the past few years, it is probable that further epidemics will occur. In the study of these, particular emphasis must be placed on elucidating the pathophysiologic processes involved, indirectly by electroencephalography, psychometric testing, personality evaluation, electromyography and careful serial physical examination, and more directly through the histologic study of biopsy material, particularly involved muscle, and by autopsy of patients dying early in the disease. Indicated also are intensive bacteriologic, virologic and serologic studies of specimens obtained early in the prodromal phase, especially among those complaining of respiratory illness in whom the full-

blown picture of the disease subsequently develops. Previous studies have too often been obliged to deal with specimens obtained many days to weeks after the insidious onset of the prodromal phase. In a community outbreak intensive study of hospital personnel, particularly nurses and student nurses, should be especially fruitful in yielding cases in greater proportionate numbers than among other groups in the population.

Although, from current reports, these illnesses do not appear numerically important on a national scale, the long-term morbidity among those who are ill and the very large percentage involved in a single outbreak indicate a need for intensive, comprehensive investigation and surveillance of outbreaks as they occur.

We are indebted to Dr. E. Charles Kunkle, professor of neurology, Duke University School of Medicine, for many helpful suggestions in the appraisal and synthesis of material.

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