The Clinical Syndrome Variously Called Benign Myalgic Encephalomyelitis, Iceland Disease and Epidemic Neuromyasthenia

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"Disease is very old and nothing about it has changed. It is we who change as we learn to recognise what was formerly imperceptible." J.M. Charcot

Recent technical advances have added greatly to the ease with which virological methods may be applied to the study of poliomyelitis and allied infection of the central nervous system. These techniques have already borne abundant fruit in the development of a vaccine against poliomyelitis. The accurate appraisal of the preventive value of such a vaccine will depend on our ability to diagnose poliomyelitis accurately. It had long been believed that the clinical features of acute paralytic poliomyelitis were sufficiently characteristic for a confident diagnosis to be made on clinical grounds alone. This confidence has recently been shaken by the finding that the virus of louping-ill (Russian spring–summer encephalomyelitis) may produce a similar clinical picture, even in the United Kingdom[1]. There is also suggestive but incomplete evidence that Coxsackie B, Echo[2] and other viruses[3] may occasionally cause acute flaccid paralysis. The position of a "non-paralytic" poliomyelitis is even less secure[4] and the diagnosis can no longer be established on clinical grounds alone.

The purpose of this article is to review a number of obscure outbreaks of paralytic illness, the majority of which were at first confused with poliomyelitis but which were later differentiated on clinical and epidemiologic grounds. Although investigations have been restricted by the fact that no deaths have occurred, the most careful virologic studies have failed to incriminate the polio virus, the Coxsackie or Echo groups of organisms, or any other known neurotrophic agent. The outbreaks will be compared, and the basis for the view that they constitute a clinical entity will be discussed. Such information as is available about the etiology, prognosis and treatment will be reviewed.

Historical

In the summer of 1934 an epidemic of poliomyelitis struck Los Angeles[5], and many of the sick patients were treated in the Los Angeles County Hospital. Within a few weeks an alarming number of cases of a similar illness had appeared among the hospital staff, particularly in the nurses. As the hospital

Figure 1

Geographical Distribution of Outbreaks

outbreak developed, certain clinical and epidemiologic features appeared which made the diagnosis of poliomyelitis difficult to sustain. Thus disturbances of sensation and mental symptoms were unduly prominent, and although muscular pain and paresis were the rule muscular atrophy was a rare sequel. In spite of the fact that no less than 198 cases developed (an attack rate of 4.4 per cent) there were no deaths, and the general trend of the disease was towards complete recovery. A further distinction from typical poliomyelitis lay in the cerebrospinal fluid, which was normal in fifty-three of fifty-nine cases studied.

After an interval of fourteen years, an epidemic with many features in common was reported in Iceland[6], and later other similar outbreaks occurred in Australia[7], Europe[8–13], the United States[14–16], Alaska[17], and South Africa[18–20]. The names "Iceland Disease" (White and Burtch 1954[14]), "Akureyri disease" (Sigurdsson and Gudmundsson 1956[21]), "benign myalgic encephalomyelitis" (Lancet 1956[22]) and "epidemic neuromyrasthenia" (Shelokov et al. 1957[15,16]) amongst others have been given to this syndrome. Of the fourteen outbreaks which form the basis of this study, no less than seven have occurred in the staff of hospitals. More than 1,000 persons are known to have been affected up to the present time. The geographical distribution of the outbreaks is shown in Figure 1.

Criteria and Definition

The difficulties in defining a disorder from which no deaths have occurred, and for which no causative infective or toxic agent has been discovered, are obvious. Recognition has to depend on the clinical and epidemiology pattern. These features must be sufficiently characteristic to separate the disorder from other conditions. A parallel may be helpful. Von Economo[23] first described encephalitis lethargica on the basis of the clinical triad of

fever, stupor and ophthalmoplegia. Although autopsy material was abundant, the pathologic picture was not in itself distinctive and the findings were often insignificant. No etiologic agent or specific diagnostic test was ever found. It was the clinical pattern and the characteristic sequelae which set the seal on the condition as a nosological entity. Epidemic myalgia (epidemic pleurodynia; Bornholm disease) affords a closer analogy. Here the disease became established as a clinical entity[24-26] in spite of the absence of mortality or any specific laboratory test long before the discovery of the Coxsackie group of viruses.

In the instance under discussion, the problem has been attacked by making a clinical and epidemiologic analysis of a number of similar outbreaks in which it has been difficult to sustain a diagnosis of poliomyelitis or any other known infection of the nervous system. All the outbreaks shared the following characteristics: (1) headache; (2) myalgia; (3) paresis; (4) symptoms or signs other than paresis suggestive of damage to the brain, spinal cord or peripheral nerves; (5) mental symptoms; (6) low or absent fever in most cases; (7) no mortality. In addition, (1) a higher frequency in women; (2) a predominantly normal cerebrospinal fluid, and (3) relapses have occurred in almost all outbreaks. In eleven of the fourteen epidemics symptoms which suggest activity of the disease have persisted for months or years in a few cases, and in eight instances there was an apparent predilection for the nursing or medical professions. Lymphadenopathy was a feature in four outbreaks.

The case for an entity will depend on the distinctiveness of these findings.

Epidemiologic Features

Of the fourteen outbreaks considered in this paper, seven occurred amongst the staff of hospitals; one in an army barracks; two in small towns; two in semi-rural communities and two in the populations of large cities. The attack rate was measured in eight outbreaks. It varied from 2 per cent in the Middlesex Hospital Nurses' Home[8] to approximately 20 per cent in the Nurses Homes at Durban[18] and Coventry[10]. At the Los Angeles County Hospital[5] the attack rate was 19.0 per cent among nurses and 4.4 per cent for all

	Table 1					
	Attack Rates by Sex					
	Males			Females		
Outbreak	Population at Risk	No. of Cases	Attack Rate per 100	Population at Risk	No. of Cases	Attack Rate per 100
Los Angeles 1934	1,779	28	1.6	2,536	168	6.4
Iceland 1948-49	3,339	171	5.1	3,548	294	8.3
Royal Free Hospital 1955	950	27	2.8	2,550	265	10.4
Punta Gorda 1956	497	20	4.0	513	42	8.4

employees, resident or living out. At the Royal Free Hospital in London[27] the figures were 18.3 per cent for nurses and 8.3 per cent for the whole population at risk. In the small communities at Akureyri in Iceland[6], Seward in Alaska[17] and Punta Gorda in Florida[16], the attack rates were approximately 6 per cent. These attack rates were much higher than usually seen in poliomyelitis.

Ten of the twelve outbreaks in the Northern Hemisphere commenced between April and September. The exceptions were the epidemic in Punta Gorda[16] which commenced in February and the small outbreak in Berlin[11] which began in November. In the Southern Hemisphere the outbreaks began in February (Durban)[19] and August (Adelaide)[7].

On the basis of case to case contact, attempts have been made to fix the incubation period of the disorder. In the Iceland[6], Bethesda[15], Royal Free Hospital[27] and Punta Gorda[16] outbreaks the evidence indicated an incubation period of less than one week, probably five to six days. In Los Angeles[5] the information on this point is incomplete, but a few patients became ill four days after their first exposure, indicating the minimum incubation period. On the other hand, the Middlesex Hospital[8] and Durban[18] reports suggested a longer period of two to three weeks. An incubation period of fourteen days was present in the single case in which isolated contact occurred in the small second outbreak in the Royal Free Hospital in 1956[13].

The general consensus is that the disorder occurs more frequently in women. (Table 1) This is certainly true of the outbreaks in hospital staffs. In the Middlesex[8], Coventry[10]

and Durban Hospitals[18] no men were affected, and only one man became ill at Bethesda[15]. In the Los Angeles[5] and Royal Free Hospital[27] outbreaks the attack rates for women were 6.4 per cent and 10.4 per cent respectively, and for men 1.6 per cent and 2.8 per cent. The higher attack rate in women on the staff of a hospital might indicate an occupational hazard rather than a true sex susceptibility. However, outbreaks in the general population confirm the higher incidence in women noted in the hospital cases. White and Burtch[14] regarded the ratio of 15:1 in favor of women in their small series as due to chance. Poskanzer and his colleagues[16] believed that in Punta Gorda, women were affected both more commonly and more severely than men. If the figures for white people and Negroes derived from their house to house survey are combined, the attack rate for women is 8.2 per cent, and for men 4.0 per cent. This female predominance is largely due to a high incidence in Negro women.

Sigurdsson[6] found that at Altureyri females were affected more commonly than males in the ratio of 8:5. All patients studied by Fog[9] in Copenhagen were female. In the Alaska[17] outbreak, the syndrome developed in 122 females and 53 males. The attack rates in these two outbreaks cannot be calculated as the population by sexes is not given. Sporadic cases[28–32] are also reported more frequently in women than in men. The single outbreak with a predominance of affected males was that described in a military barracks in Berlin[11]. The patients were all men.

All age groups have been affected from late childhood[6,14,16,17] to the eighth decade[16]. However, many reports stress the high frequency among young adults. In the Los

Angeles outbreak[5] the figures show a strikingly selectivity of the disorder for women between the ages of twenty and twenty-nine. In men the relationship to age was irregular. In the Middlesex Hospital[8], Coventry[10], Durban[18], Bethesda[15] and Berlin[11] outbreaks most of the cases occurred in the third decade, but this may be due, in part at least to the composition of the population at risk. Figures from which attack rates may be calculated by age are not given. In the Royal Free Hospital outbreaks[12,13] the incidence was higher in the nineteen to thirty-five age group (11 per cent) than in older people (4 per cent). In Iceland[6] the highest incidence was in adolescents aged fifteen to nineteen. Cases in small children have been rare.

A prevalence of poliomyelitis in the area of the outbreak has been noted on several occasions and has made differential diagnosis difficult. The most striking example is the Los Angeles outbreak[5] of 1934. There the cases among the staff occurred after the admission of large numbers of patients with poliomyelitis from the city and the rise and fall of the epidemic in the city corresponded closely with that of the hospital outbreak. Virus studies and autopsy material proved that the city epidemic was poliomyelitis, although there were certain atypical features[5].

However, the clinical characteristics in the cases among the staff differed in important particulars.
Coincident outbreaks of poliomyelitis also occurred in Copenhagen[9], New York State[14] and Alaska[17]. In Adelaide[7] and Durban[18], epidemics of poliomyelitis preceded the outbreaks of illness and in Iceland[6] there were

a few cases of typical poliomyelitis at the beginning of the outbreak. At Coventry the outbreak occurred amongst the staff of an infectious diseases hospital which was commonly concerned with the treatment of poliomyelitis. In the Middlesex[8], Bethesda[15], Royal Free Hospital[12], Berlin[11] and Punta Gorda[16] outbreaks there was no known association with poliomyelitis.

Most curious of all the epidemiologic features is the apparent susceptibility of the nursing medical and ancillary processions. Seven of the fourteen outbreaks have occurred in the staffs of hospitals. In one other[16] a high attack rate among nurses, doctors and their helpers was noted. Thus the attack rate among medical personnel was 40 per cent (sixteen of thirty-eight) as opposed to 6.1 per cent (62 of 1,010) in the community as a whole. In the Los Angeles[5] and Royal Free Hospital[12] outbreaks the attack rates were higher in nurses than in the other hospital staff. In theMiddlesex[8], Coventry[10], Bethesda[15] and Durban[18] epidemics the disorder was virtually confined to nurses.

It is recognized that nurses through contact with patients have an increased risk of contracting certain infections. As far as this syndrome is concerned, however, there has been evidence that the nurses might have been infected by patients in only two outbreaks[5,10]. Thus in Los Angeles cases occurred both earlier and more commonly in those members of the hospital staff who were in close contact with patients with poliomyelitis who had been admitted from the city. On the other hand the clinical evidence suggests that the illness among the staff was different. In the Coventry

Hospital[10], the disorder may have reached the staff by way of the patients. Galpine and Bradley[32] were of the opinion that some of the cases admitted immediately prior to the outbreak in the staff in Coventry were not poliomyelitis but an illness identical with that which affected the staff. In the remaining five institutional outbreaks there is no evidence that nurses were infected by patients. Spread in the reverse direction (nurses *to* patients) has either been extremely uncommon[12,15] or absent.

This apparent predilection for medical personnel, particularly nurses, remains one of the most difficult and interesting features of these outbreaks. It should be recalled, however, that a high standard of diagnostic skill is usually available to nurses, and that similar outbreaks in other types of residential institutions may have been unrecorded.

Observations concerning the possible mode of spread are available in nine outbreaks. In eight there is good reason to suppose that the agent responsible was not food- or water-borne. The distribution of cases did not correspond with any source of water or food. In the Iceland outbreak spread occurred along the main traffic route from Akureyri. Instances of spread by personal contact have been recorded[8,13,27] and most authors agree that this is the probable means of dissemination. The best authenticated example is cited by Crowley[27]. A nurse who had attended the first and fourth girls to fall sick in the Royal Free Hospital epidemic became ill six days later. During the incubation period "she had accompanied a surgical case from ward to operating theatre, remained in attendance during the operation, and escorted the case to bed in a different ward. The patient,

the ward sister, the theatre sister, a medical officer, a medical student working in the theatre and the second ward sister all became ill within eight days." In the Bethesda outbreak[15] the discovery of a paracolon organism in the stools of a large proportion of the affected nurses and in a kitchen attendant focussed attention on the possibility of food-borne infection. However, only one doubtful case developed among the patients who were also supplied with food from the same source. The world-wide distribution of the outbreaks (Fig. 1) together with the marked differences in the types of community affected are points against either an insect vector or a toxic agent, both of which have been sought without success.

Clinical Features

An exact numerical comparison of the symptoms and signs reported in the various outbreaks is not possible. Thus in some instances only cases selected on the basis of severity or convenience were examined in detail[6,9,14,16] while in others[5,8,12] an over-all picture of the outbreak was provided. Reports of the Durban epidemic are fragmentary, and it has been necessary to refer to unpublished data[18]. The description of the Adelaide epidemic[7] differs from the rest of the material in that it refers only to cases which were admitted to an isolation hospital from an urban community. Presumably, this would bias the material in favor of severe cases.

Broadly speaking, the epidemic cases have fallen into two groups: patients with definite localised muscular paresis, and those without. Only the former will be described in detail, as

it is doubtful whether the latter could be distinguished from many other illnesses in the absence of an epidemic. The frequency of paretic cases in the various outbreaks has varied from about 10 per cent in the Punta Gorda outbreak to 80 per cent in Los Angeles. An approximate over-all figure is 40 per cent.

Mode of Onset. The onset of the illness has usually been abrupt. According to Gilliam's detailed reports the onset in the Los Angeles cases was sudden, the most prominent early symptoms being headache and muscular pain, both of which occurred in over two-thirds of all cases during the first three days of the illness. Next in frequency were nausea, which occurred in about half the cases, and sensory disturbances, stiffness of the neck and back in about one-third. Fever, with a temperature in excess of 100°F., was found in only a quarter of all cases and in almost all of these it appeared on the first day of the illness. Muscular tenderness and localised pareses were uncommon initial symptoms, but by the end of the first week they had developed in about half the cases.

In the Akureyri outbreak[6] pains in the neck and back were almost universal in the first few days of the disease. Low fever was also common. Within a few days pains accompanied by parenthesias appeared in the limbs. In the more severe cases fibrillary twitchings of muscles were also noted. In the paralytic cases paresis usually appeared three to seven days after the onset.

According to White and Burtch[14] the onset of illness in the Thousand Islands district of New York State was acute in four and insidious in fifteen of the cases selected for detailed study. The average duration of symptoms prior to the initial examination was twenty-one days. In retrospect, the commonest presenting symptoms were found to have been muscle pain and headache associated with low fever. Coryza, sore throat, cough, nausea and diarrhea were also noted during the first few days. An exact account of the time of onset of paresis was not given, but it seemed likely from the two "representative case reports" that it did not occur before the end of the first week.

In the Adelaide epidemic[7] the onset was abrupt with stiffness and backache. Headache, pain on moving the eyes, malaise, aching in the limbs and hyperpathia were other common early symptoms. It should be recalled, however, that only patients sufficiently ill to be admitted to an isolation hospital from a city were dealt with in this report, a striking contrast to the selection of the New York cases.

In the Middlesex Hospital outbreak[8], like the other epidemics involving hospital staffs, the whole population at risk was under close medical supervision throughout. In most cases symptoms appeared abruptly. Headache, malaise and backache were almost invariable, and pain in the limbs occurred early in ten of fourteen cases. Mild pyrexia was present at the onset in nine cases. Vomiting and diarrhea occurred infrequently. In one case there was a definite biphasic illness similar to that which is seen in poliomyelitis.

According to Fog[9] headache associated with low fever was an invariable initial symptom in the Copenhagen patients. In a few it was accompanied by stiffness of the neck or back,

nausea, vomiting, dizziness and pain in the limbs.

In the Coventry epidemic[10] the preparetic symptoms were usually insidious and insufficiently severe to make the patients report sick before the onset of paralysis. The premonitory symptoms included sore throat, headache, backache, nausea, chills and lethargy. Paresis developed from two to thirteen days after the onset of these symptoms, usually on the sixth day. In only six of the thirteen patients was fever noted after reporting sick and in none of these did it exceed 100°F.

In their description of the Bethesda outbreak, which occurred in the staff of a psychiatric hospital, Shelokov and his colleagues[15] confined their detailed description to the twenty-six confirmed paretic cases. Twenty-one of these patients presented with premonitory symptoms before the onset of paralysis. The proximal illness was characterised by malaise, headache, aches and low grade fever, which lasted from four to six days. Sometimes there was an interval of apparent well-being between the prodomal illness and the paretic manifestations. Occasionally, the prodomal illness was prolonged by the appearance either of acute respiratory or gastrointestinal symptoms, namely, cough, diarrhea nausea and vomiting.

In the small outbreak in an army barracks in Berlin[11] the patients presented with abrupt onset of headache and low fever. Three days later muscular pains, backache and photophobia appeared.

According to Adamson most of the patients amongst the staff of the Durban Hospital became ill with severe occipital headache, stiffness of the neck, back-ache and weakness of the muscles of the back and abdomen. Heaviness, weakness and parenthesias in a limb or limbs followed within twenty-four hours. Prodromal symptoms of lassitude, sore throat, vomiting and diarrhea in the preceding ten to fourteen days were sometimes volunteered by the patient, but more frequently were ascertained only by direct questioning. It would appear, therefore, that the proximal illness in this outbreak was mild in most cases. According to Hill[19] coryza and sore eyes were also occasional prodomal features.

Both in size and in the wealth of clinical detail reported, the Royal Free Hospital epidemic[12] compares with the Los Angeles outbreak of 1934. The following presenting symptoms occurred in at least a third of the 200 patients in whom records were complete. In order of frequency they were headache, sore throat, malaise, lassitude, vertigo, pain in the limbs and nausea. A striking feature was the intensity of the malaise, which was out of proportion to the slight pyrexia. In only nine cases (4.5 per cent) was a temperature over 100°F recorded. On examination the superficial lymph nodes of the neck were enlarged in almost every case, particularly in the posterior triangle. Paralysis and other neurological signs developed toward the end of the first week in many cases. The small second outbreak affecting the Preliminary Training School of the same hospital a year later[13] had a similar pattern of onset.

According to Poskanzer and his colleagues[16] the onset of the Punta Gorda outbreak was insidious, and was marked by fatigue, headache, pains in the back and limbs, depression and instability. The average period between onset and confinement to bed was nineteen days with a range of one to sixty-five days. In half the patients there was a sudden exacerbation of symptoms one to four weeks after the onset.

The Fully Developed Acute Illness. Gilliam's[5] account of the Los Angeles outbreak is of particular interest, not only because of the richness of the clinical detail but because it is the first definitive description of the illness in the literature. The postwar European Icelandic, Adelaide and Durban epidemics were recorded without knowledge of Gilliam's findings and are unbiased by his interpretation of them. The Los Angeles outbreak therefore affords an ideal basis for comparison with later epidemics.

Severe generalised headache was almost invariable (94 per cent) and was accompanied by some stiffness of the neck or back in two-thirds of the patients. Pain in muscles was also an almost constant feature. The common sites were the neck, shoulders and limbs. It varied in intensity, both from case to case and from day to day, and was usually aggravated by exertion. In severe cases it was agonising and unresponsive even to opiates. When severe it was accompanied by exquisite muscular tenderness, tender nerve trunks and by skin sensitivity so that the affected limb required cradles to prevent contact with bed clothes. Muscular twitching, sometimes sufficient to move a whole extremity, was noted and cramps were frequent. Definite parenthesias occurred

in 42 per cent of the cases. Low fever with temperatures which uncommonly rose above 100°F accompanied these symptoms during the first few days.

Localized muscular weakness developed in 80 per cent of the cases. It was notably variable both in site and in intensity from day to day. Of a total of 152 paretic cases, the weakness was noted within the first thirteen days in 119. In about half it had cleared within four weeks, and in a further 25 percent within eight weeks. In 12 per cent demonstrable paresis was present three months after the onset.

There is a notable absence of information about the changes in tone sensation and deep reflexes associated with the paresis. Gilliam admits that full neurological examinations were rarely performed; this was doubtless due partly to the pressure of the epidemic. More important perhaps is the fact that orthopedic surgeons rather than internists had much of the clinical responsibility. As it was, patchy anaesthesia was noted in a few cases diplopia in thirty-one, facial paresis in three and difficulty in swallowing in six. Other cranial nerve symptoms or signs were found in eleven patients. True vertigo was rare and hyperacusis and deafness were not recorded. Two patients required treatment in a respirator for a short time.

Urinary retention requiring catheterization was a complicating feature in 12 percent. It was frequently accompanied by constipation. Although these symptoms developed only in the paralytic cases following total immobilization in Bradford frames, Gilliam was satisfied that the time relationships showed

that they were a real part of the illness and not an artifact introduced by the mode of treatment.

Gilliam observed the mental symptoms which have been an almost constant feature of more recent outbreaks. Later writers have also shared his perplexity in assessing their significance. In the Los Angeles outbreak they occurred in 30 per cent of the patients. His original description of them deserves direct quotation. "The emotional upsets reported are difficult to interpret. They varied in degree from relatively slight displays of irritability and impatience to violent manifestations of dislike for people and things formerly liked. A common type of upset consisted of crying spells resulting from no known provocation. The emotional upsets of a few individuals were undoubtedly hysterical in nature, but it would be manifestly erroneous to consider as hysteria the emotional instability associated with this illness in all of the cases in which it was present. Other disturbances chiefly consisted of loss of memory and difficulty in concentration. Transient personality changes of varying degrees of severity were relatively common." Coma and reversal of sleep rhythm did not occur. After running a course of four to eight weeks the illness abated and paresis disappeared in most cases. However in some cases one or more well defined relapses occurred. The average period of hospitalization was eight weeks.

In the Iceland outbreak[6] paresis was usually confined to a single muscle group, the abductors of the shoulders and the abductors and rotators of the hip being the most commonly affected. Paresis was accompanied by an exacerbation of pain and tenderness in the muscles concerned together with

parenthesias. In severe cases, hyperpathia or anesthesia developed in the affected limb. Coarse muscular twitching was common, but true matriculation was absent. The paralysed limb was always hypotonic, although reflex changes were reported as variable. Extensor plantar responses were not noted. Cranial nerve palsies were rare and urinary retention was reported in two cases only. Emotional lability, irritability, depression and lack of concentration appeared in convalescence and were extremely troublesome. The duration of the illness in the milder cases was from two to four weeks and in the more severe cases from two to three months.

In the New York state cases[14], muscular aching often accompanied by head or neck ache was the most consistent symptom. It affected the muscles of the shoulder girdle in seventeen of nineteen cases at some state of the illness, but other muscles were usually involved and pleuritic chest pain was also reported. The aching was invariably accompanied by muscular tenderness and usually by hyperpathia and parenthesias. Muscular weakness, which was common, never coincided with the distribution of the tenderness. The deep tendon reflexes were usually reduced in the weak limb, but atrophy did not develop. Sensory loss was noted in three cases. Marked mental depression occurred in eleven of the nineteen subjects studied.

In the Adelaide outbreak[7] the acute illness was short. Following the development of severe headache and mild generalized muscular aching, widespread paresis occurred. It cleared rapidly after a few days. Cranial nerve palsies,

parenthesias and hyperpathia were rare. Retention of urine occurred in a number of cases. A recrudescence of the disease, characterized by hyperacusis, depression and fatigue, often occurred four to eight weeks after the original illness. It was protracted and resistant to treatment.

In the Middlesex Hospital outbreak[8] the characteristic features were "the association of severe muscular pain affecting the back, limbs, abdomen and chest with evidence of mild involvement of the central nervous system in which the weight of the damage appeared to fall on the pyramidal tracts, the posterior columns, and the cranial nerves rather than on the anterior horn cells". Following the prodromal symptoms already described, nine of the fourteen patients experienced sudden onset of pain, tenderness, spasm and paresis in the muscles of a limb or limbs associated with parenthesias and hyperpathia. The discomfort was always sufficiently severe to require full doses of analgesics for relief. Any handling of the limb at the bedside was resented and the patient could not bear the weight of the bed clothes upon it. The paresis was usually most marked in the distal muscles and was accompanied by variable reflex changes. The plantar response was frequently extensor on the paralysed side and loss of vibration sense was common in affected limbs. Pleuritic chest pain and urinary retention and incontinence were also prominent features. In the cranial nerves nystagmus was almost invariable, and vertigo, deafness and paresis of the soft palate were also reported. One patient was nursed in a respirator for a short time. In most cases the muscular pain and paresis had disappeared by the end of the third week. Relapses in the second and third weeks occurred in a few cases. Emotional disturbances were common in the acute stage, but did not persist into convalescence[8a].

In Copenhagen[9] the fully developed syndrome was characterized by severe pain and unpleasant paresthesias in the extremities. Definite paresis associated with increased deep reflexes was present in one patient and weakness and clumsiness in several others. Hyperhidrosis and muscular tenderness also occurred in the affected limbs. Nystagmus, diplopia, ptosis and extensor responses were each noted on one occasion. Depression and mental lability were prominent.

In the Coventry cases[10] the onset of paresis was a coupled with an exacerbation of headache and pain in the neck and usually first manifested itself by clumsiness and heaviness of a limb. Muscular pain occurred but does not appear to have been severe. Chest and abdominal pain are not described. Tenderness, unsteadiness in response to effort and hyperpathia were often noted. Temporary loss of position sense was found in four patients. The deep reflexes in the affected limb were usually diminished and the plantar responses were flexor. Difficulty in micturition was noted in fur cases. Recovery took place in some instances within a month, and in all cases was substantially complete within two months. Lack of concentration and ability to memorize was described as a characteristic symptom in convalescence.

Shelokov's[15] description of the Bethesda outbreak resembles the Coventry epidemic in many ways. The onset of paresis was heralded

by an exacerbation of the headache and stiffness of the neck, together with heaviness and numbness in one or more limbs. Myalgia and muscular tenderness were invariable in the paralysed limbs and pleuritic chest pain was also noted. Paresthesias were common and were sometimes accompanied by changes on formal sensory testing. Nervousness, unprovoked crying spells, difficulty in concentration, undue irritability and anxiety occurred in nineteen of twenty-six patients studied in detail. Nausea, diarrhea, somnolence and insomnia were unusual manifestations of this outbreak. Cranial nerve palsies were not mentioned.

In the Alaska outbreak[17] muscular pain was accompanied by photophobia, hyperacusis, disturbances of taste and extreme anxiety. Paresthesias were common. Use of the affected muscles exacerbated the pain, but marked muscular tenderness did not occur. Tremors in the acute stage were a bad prognostic sign as far as the subsequent development of paralysis was concerned. Muscular weakness was widespread and commonly affected one or the other side of the body exclusively. Incoordination and myoclonic jerks were also seen, and constipation and transient urinary retention were common.

The clinical account of the small Berlin outbreak[11] is incomplete. Severe pains in the limbs with muscular tenderness were invariable. Paresthesias and other sensory changes are not mentioned. Slight muscular weakness unaccompanied by reflex changes developed in three of the seven cases and hyperacusis in two. Depression was a feature in three patients and persisted into convalescence.

Conjunctival injection ocurred in five patients and an erythematous rash in two.

In the extensive outbreak among the nurses at the Addington Hospital, Durban[18–20] the onset of paresis, backache, shoulder girdle and subcostal pain followed an ill-defined period of prodromal symptoms. Headache, if pre-existing, became very severe at this stage. Weakness of the abdomen and back were so common that the inability to sit up from the supine posture became an important early diagnostic sign. Paresis in a limb was usually accompanied by paresthesias and patchy sensory loss. Posterior column signs were also noted. The deep reflexes were usually altered in a paralysed limb. Although the plantar responses were equivocal on a number of occasions, they were never frankly extensor. Retention of urine occurred in ten cases. Affection of the cranial nerves was rare[19] and was limited to a few instances of facial paresis and perceptive deafness. Mental symptoms were prominent, particularly in the severer cases and included defective concentration and memory, drowsiness, emotional instability and nightmares. In the majority, full recovery occurred within two months. Muscular atrophy was never observed.

In the epidemic at the Royal Free hospital[12] no clear division of symptoms into those appearing early and late was possible. Neurological manifestations appeared most commonly in the second and subsequent weeks of the disease, but occasionally in the first. The fully developed clinical picture consisted of pain in the neck, back, subcostal region or limbs, out of all proportion to the degree of pyrexia, and general constitutional disturbance,

and dizziness. The intensity of the symptoms fluctuated widely from day to day but on occasion the pain required the strongest analgesics for relief. Pyrexia rarely reached 100°F., and there was little tachycardia. Tender enlargement of the cervical lymph nodes was almost invariable. The liver was palpable in 8.5 per cent of cases.

The neurological symptoms and signs which developed in 148 (74 per cent) were believed to form "a characteristic picture that distinguishes this disease from other infections of the nervous system". Hypersomnia, nightmares, panic states, uncontrollable weeping and amnesia were frequent symptoms in the acute state. In six patients severe mental illness developed in which the dominant feature was depression. Two of these had to be committed and subsequently were treated with convulsive therapy; a third took her own life. Cranial nerve lesions occurred in sixty-nine of the 200 fully documented cases, the ocular, facial and acoustic nerves being most commonly affected. Bulbar palsy appeared in eleven cases.

In the limbs motor weakness occurred in 102 patients and sensory disturbances in eighty-two. The paresis was almost invariably accompanied by pain and marked muscular tenderness and the slightest attempt at active or passive movement was resented. Cutaneous hyperpathia parenthesias and loss of position and vibration sense were common accompaniments. Spasm, matriculation and myoclonic jerks occurred less frequently. The paresis was usually most marked in the peripheral muscles and was commonly of hemiplegic distribution. The deep tendon reflexes were sluggish in the early stages and exaggerated later in the disease. They were never abolished. Frank extensor plantar responses occurred in two cases only, but equivocal or absent responses were common. Muscular wasting occurred in two cases. Bladder dysfunction, including retention of urine, developed in one-fourth of the patients. In the phase of recovery, jerkiness of the paretic limbs in response to voluntary movement was noted and considered to be characteristic. (A similar phenomenon was also noted in the Coventry and Durban outbreaks.)

The clinical picture of the Punta Gorda outbreak[16] was described on the basis of the findings in twenty-one of thirty patients interviewed between May 24 and June 6, 1956, "who presented similar histories of illness, and had no major undercurrent medical problems". It will be recalled that these patients had been ill with vague symptoms for periods ranging from one to sixty-five days. The most prominent general symptom was fatigue coupled with headache, pain in the neck, nausea and vomiting. Depression and impaired memory was present in nineteen and was associated with terrifying dreams and episodes of crying without provocation. Symptoms suggesting involvement of the central nervous system consisted of parenthesias, unsteadiness, vertigo, blurring of vision and diplopia. The account of paresis is confusing and is recorded as present in eight cases in the text, and in only two cases in the accompanying table. In any case, it appears to have been mild and localized, and other neurological signs were absent. It seems that the illness in Punta Gorda ran a subacute rather than an acute course, and that objective evidence of disease was minimal.

Status of Patients on Discharge from Hospital. In addition to formal follow-up studies, some information is available about the state of health of the patients on discharge from the hospital, and in the case of nurses, about the total time lost from work.

According to Gilliam[5], the average period which elapsed from the onset of illness to return to duty in Los Angeles was 13.6 weeks, but this figure is based on less than half the cases, as 55 per cent of the patients were still on the sick list at the time of his report. When he last observed them, forty-three patients (22 per cent) still had definite localized paresis, and in eighteen this was moderate or severe. Muscular atrophy was a rare sequel and in the ten cases in which it was noted it was slight. He stated that the irregularities in the course of the disease and the peculiarities of the paresis forbade an accurate estimate of the recovery rate.

Adams[18] gives an account of the disability rate in the Durban Hospital outbreak six months after the appearance of the last case. Of ninety-eight nurses, fifty had returned to full duty with no apparent sequelae, and a further thirty-two were on duty with "mild or more serious residua". Seven were on sick leave with serious sequelae, seven were on vacation or had resigned, and two had been readmitted to the hospital in relapse. In mild cases full recovery of muscular power occurred within a few days and convalescence, which was punctuated by headache, aching and fatigue, was complete within a month. In moderate cases the return to normal took three to four months. In the severe cases which fortunately were few, relapses

were continuing up to seven months after the onset.

In the Royal Free Hospital outbreak[8], the duration of hospital in-patient treatment was less than one month in 57 per cent; from one to two months in 28.5 per cent; from two to three months in 7.5 per cent and more than three months in the remaining 7 per cent. Convalescence was very prolonged, "and extreme fatigue and general aches and pains made the rehabilitation period extremely tedious and long". A period of six weeks convalescence was found necessary for patients who had been in bed for more than a month. Even when this was completed many patients could work only four hours a day. Four patients still had marked disability at the time of the report, two years after the epidemic. In one patient choreoathetoid movements had developed in her paralysed right hand; two required leg callipers and a fourth crutches.

In the Middlesex Hospital outbreak[8], seven of the fourteen patients showed no physical signs of disease on discharge from the hospital on an average of one a month after the onset. Of the remainder, four showed mild pyramidal tract involvement, one had absent position and vibration sense in the right foot, another had mild bilateral deafness of the inner ear, and a third had patchy anesthesia involving the left thigh with marked tenderness of the underlying muscle.

The Aftermath. Relapses: The majority of patients afflicted in these outbreaks have been discharged from the hospital within two months and have returned to work after a period of convalescence prolonged by fatigue,

aches and pains, depression and lack of concentration. However, in a proportion which has varied from outbreak to outbreak, relapses or a chronic state of ill health have developed.

Relapses have been a feature of all outbreaks except one (Coventry). They have usually occurred within a week or two of the initial illness, while the patient was still in the hospital, but in some instances they have necessitated second admission to the hospital. In the need York State cases[14] the timing of the relapses was not described, but they are mentioned indirectly as a feature in common with the Iceland outbreak. In the Punta Gorda outbreak the course was subacute from the onset and exacerbations, rather than relapses, occurred. In five outbreaks[5,9,15,16,17] relapses or exacerbations of symptoms in women have coincided with menstrual periods. Physical exertion and cold weather have also been incriminated. Most reports indicate that the chance of relapse diminished with the interval after recovery from the initial illness and that recurrences are rare after the end of the third month. However, Deisher[17] described cyclical recurrences in many of his patients up to two and a half years after the first illness, but it is not clear whether these were relapses in apparently healthy people or repeated exacerbations of chronic symptoms. Galpine and Brady[32] have described a second attack three years after a previous similar illness. There had been complete recovery in the interim with perfect health.

The relapses have consisted either of a return of paresis to areas previously affected, or to fresh areas, accompanied in some cases by fresh neurological signs, or simply of fresh muscular pains or mental symptoms. Fever is a frequent but not invariable accompaniment. Little has been added to Gilliam's original description, "Following a recrudescence of constitutional symptoms there was frequently an extension of pain or weakness into muscle groups not previously involved. In many cases the constitutional symptoms during the recurrences were considerably more severe than at onset… The milder "relapses" were sufficiently annoying that all convalescents were constantly "keyed up"" in fear they would develop one. There appeared to be no predisposing cause for them, though in many they were associated with untimely overexertion or with some phase, usually the onset of menstruation. Cold damp weather frequently increased pain and a sense of illbeing in patients in whom a definite recrudescence was not precipitated. A few of the "relapses" were unquestionably hysterical in nature." It is interesting to compare the description of relapses in the Royal Free Hospital outbreak, which was written without knowledge of Gilliam's account. "There might be periods of two weeks in which the symptoms were mild and fever had disappeared. Such periods were often followed by marked recrudescence of old symptoms and sometimes by the appearance of fresh neurological manifestations. In such relapses further fever and tender enlargement of glands occurred. Relapses occurred in some cases after patients had been fit enough to return to their homes… Functional manifestations in a few cases overlaid the organic picture, particularly in those cases longest in hospital."

The subacute and chronic stages: In seven of the recorded outbreaks a proportion of the

patients has been followed for periods of months or years. Once again the methods of selection have varied and prevent an accurate assessment of the comparative incidence of sequelae and chronic cases. In the Iceland epidemic, fifty-seven (12 per cent) of the 465 patients originally affected at Akureyri were examined seven to ten months after the onset[6]. These patients were not representative of the epidemic as a whole, as 74 per cent of them had been paralyzed whereas the paralysis rate for the whole outbreak was only 28 per cent. Six years after the outbreak Sigurdsson[21] examined thirty-nine of these fifty-seven patients again (thirty-three women and six men) and reported his findings. There is no information as to what had happened to the remaining eighteen. It seems reasonable to suspect that a bias was operating in favor of patients with continued symptoms. The grounds for the selection of eight of nineteen patients for re-examination fifteen months after the New York State outbreak[14] and twelve of fifty patients six months after the Bethesda epidemics are uncertain.

The follow-up studies in the Alaska[17] and Punta Gorda[16] outbreaks are important because all patients originally examined were traced and studied after the elapse of two years in the former, and of five months in the latter.

Seven to ten months after the Akureyri outbreak, Sigurdsson and his colleagues[6] found that most of the fifty-seven patients whom they examined had returned to work. However only six were free of symptoms. Among the remainder, nervousness, fatigue and persistent muscular pains were common and eleven complained of mild paresis. On examination, nineteen of the patients were found to be free of all objective evidence of disease but in the rest there was a confusing mixture of signs, some of which were thought to represent organic disease and others to indicate hysteria, Localized muscular tenderness was found in nineteen, Paresis in sixteen, muscular atrophy in fourteen and sensory changes in twelve.

Six years later, thirty-nine of these patients were examined again[21]. All had returned to their previous occupations (except one who was suffering from a gastric ulcer) but only five considered themselves completely recovered. Of the remainder, twenty-eight complained of nervousness and tiredness, twenty-four of muscle pains and eight of loss of memory. Sleeplessness and parenthesias occurred less frequently. Muscular tenderness was found in ten, paresis in nine, and atrophy in six. Unfortunately, both these follow-up studies are lacking in any description of changes in tone, coordination or reflexes.

Two to three years after the acute illness, Pellew[33] interviewed the five Adelaide patients who had originally been chosen for serological studies. In all, there had been emotional instability or lack of concentration for eighteen months to two years, and in four, muscular pains had also been a feature. All five had improved and were well at the time of interview.

Fog[9] describes the enormous fluctuations in symptomatology in his Copenhagen patients during the first two to three months of the illness. Six months after the outbreak, three of the ten patients had returned to their occupations, three were working part time, two were convalescent and two were still in the

hospital. None were free of symptoms, but all had improved.

In the Bethesda outbreak[15], none of the twelve patients selected for re-examination three to five months after the onset felt well, although they considered that they were improving slowly. They complained of recrudescences of low grade fever, myalgia, chest pains and localized weakness.

Interrogation of the Punta Gorda patients[16] five months after the original study demonstrated a paucity of signs as compared with symptoms, an over-all tendency towards slow improvement and a fluctuating course. Only one patient was completely well. In the remainder there had been periods of improvement interrupted by exacerbations of symptoms with a definite trend towards recovery. Thus, whereas in the second month of the disease more than half of the patients were confined to bed, only three were thus confined in the sixth month. Symptoms remained common; nervous tensions in eighteen, fatigue in fifteen, and depression in twelve. On the other hand, objective evidence of mental tension (the criteria are not described) was found in only one case. Diminution in sensation was found in ten patients, muscular tenderness in seven and paresis in one.

Deisher[17] appears to have had the unusual opportunity of re-examining all his 175 patients two years after the onset of the illness. Unfortunately, the information derived was incomplete; there are no data available about the number who were free of symptoms or the number who had been unable to resume work,

and no description is given of reflex and sensory changes. Of the 175 patients, 110 complained of tiring easily, eighty-one of pain and stiffness, and fifty-seven of muscle weakness (as distinct from "paralysis", which was present in sixteen cases). Emotional instability, tension, poor concentration and memory defects were extremely common. Tremor, incoordination and muscular jerking were also seen.

Summary of the Clinical Features. In all outbreaks prodromal symptoms preceded the development of paresis or other neurological signs, but their severity and duration varied. In eight, the prodromal illness was well defined, and lasted about a week. In the Coventry and Durban cases it was mild and most of the patients presented for treatment in the paretic phase. In the Berlin outbreak the prodrome was sharp but abbreviated, lasting three days. The Punta Gorda outbreak differs in the length and vagueness of the premonitory phase. Most of the patients were not confined to bed until the end of the third week. Information about the length of the prodromal illness in the New York and Alaska cases is incomplete.

Headache has been reported as a presenting feature in all outbreaks and pain in the neck, back and limbs are also common early symptoms. These complaints and the malaise which accompanies them have been out of proportion to the fever, which is usually slight even at the onset and sometimes absent[8,12,15,16]. Symptoms of an upper respiratory or gastrointestinal disturbance (sore throat, coryza, nausea, vomiting, diarrhea) may also develop at this stage. A definite intermission between the prodromal symptoms and the

paretic illness is rare, and has been reported as a constant feature in only one outbreak[15].

Muscular pain, headache or pain in the neck, and paresis have been features of the fully developed syndrome in all outbreaks. In the worst Los Angeles, Middlesex and Royal Free Hospital cases, the myalgia has been agonizing, requiring administration of narcotics for its relief. Its variability both in site and in intensity from day to day has been remarked on a number of occasions. Pain in the limbs has occurred at some stage in most cases, but pain in the shoulders, chest and abdomen is also a prominent feature, and has raised the question of a Coxsackie infection. In the New York State and Coventry cases the discomfort in the limbs scarcely amounted to pain.

With the exception of the New York cases the distribution of the paresis has followed that of the muscle pain and tenderness. Numbness, tingling and in some cases deficiencies of sensation on formal testing have been a feature of all outbreaks except one[11], and usually occurred in limbs affected by paralysis. Hyperpathia, muscular spasm, cramps, tremors and involuntary movements were noted in severely affected patients in about half the outbreaks. The deep reflexes in the paretic limbs may be hyperactive or depressed, but are rarely if ever abolished. Frank extensor plantar responses have been unusual, but equivocal or absent responses are relatively common. Retention of urine requiring catheterization or incontinence has occurred in eight outbreaks, and urinary frequency was a feature of one other.

Symptoms or signs indicating damage to the cranial nerves or their central connections have occurred in nine outbreaks. In six they were uncommon, but in the Royal Free Hospital, Middlesex and Los Angeles cases they were relatively frequent. Diplopia, facial paresis, tinnitus, vertigo, inner ear deafness and bulbar involvement have all been reported. Hyperacusis was a feature of no less than five epidemics[7,8,11,12,17]. Nystagmus was almost invariable in the Middlesex Hospital and Berlin patients, common in the Royal Free Hospital cases, and an unusual finding in four other outbreaks. Mental disturbances, of which depression, emotional lability and lack of concentration are commonest, have occurred in all reported outbreaks. In most instances they appeared during the acute illness[5,8,12,14–18] but in others they first became manifest during convalescence[6,7,10].

Lymphadenopathy was first reported by White and Burtch[14] in four of the New York State cases. It also occurred as a rare feature in the Durban and Middlesex Hospital cases. In the Royal Free Hospital outbreaks it was such a constant feature that the illness was at first diagnosed as infectious mononucleosis. Hepatic enlargement was also noted in a few of these cases.

In most patients recovery has been complete within one to two months. However, in a proportion, which has varied from outbreak to outbreak, the course has been punctuated by relapses. These have involved simply a return of pain and fever in some instances, in others, fresh paresis and other neurological signs, or mental disturbances. In general, even in these patients there has been a trend towards

improvement but in some instances a characteristic syndrome of chronic ill health has developed, with cyclical recrudescences of pain, fatigued weakness and depression, often coincident with menstruation, cold weather and exertion. Objective neurological sequelae, such as muscular atrophy, involuntary movements, sensory loss, deafness and incoordination have occurred in a small minority.

Sporadic Cases

In addition to epidemics, sporadic cases with the familiar clinical features have occurred. The first endemic case in which a diagnosis of "Iceland disease"' was made was reported by Hardtke[28]. He described the illness of a forty-one year old female physiotherapist in Indiana in October 1953. She presented with headache, stiff neck, pain in the shoulders and limbs, and incoordination. Within a few days she found that attempted movements or the slightest jolting precipitated agonizing cramp-like muscular spasms against which her only defense was absolute immobility. She was admitted to the hospital as a poliomyelitis suspect and on examination was found to have questionable weakness of the lower left side of the face and exaggerated unequal reflexes. The cerebrospinal fluid was normal and in the absence of any flaccid paralysis, a diagnosis of poliomyelitis could not be sustained. A relapse occurred in February 1954, and when examined in July she was found to be depressed, with loss of memory and absent gag reflex on the right, diminished sensation on the left side of the body and persistence of the reflex abnormalities already described. Coxsackie infection was not excluded in this instance, although the combination of neurotoxic signs

with a normal cerebrospinal fluid and a chronic course make this diagnosis unlikely.

In 1956 Ramsay and O'Sullivan[29] reported on eight patients admitted to the Infectious Diseases Department of the Royal Free Hospital from the population of northwest London between April and October 1955, before, during and after the extensive epidemic in the staff of the main hospital. None of these patients, of whom seven were female, had been in contact with the sick nurses.

The onset was generally gradual with headache, pain in the limbs, giddiness and upper respiratory or gastric symptoms. Fever rarely exceeded 100°F. Earache, tinnitus, cramps, muscular twitching, tremors and parenthesize were also noted. On examination, lymphadenopathy occurred in seven; stiffness of the neck, paresis and exaggerated deep reflexes in six; sensory impairment and muscle tenderness in five; and cranial nerve involvement in four. Extensor plantar responses were noted in three cases. Convalescence was protracted. In four cases it was complicated by emotional disturbances. Full virological studies, including the use of tissue culture methods, were carried out in all eight cases and were negative.

Jellinek[30] described two patients on the staff of hospital in Hampshire who suffered from a similar illness in the summer of 1955. Both were females, one a doctor and the other a nurse. Both had headache, stiffness of the neck, fever, myalgia and a variety of neurological signs including nystagmus (two), facial weakness (one), exaggerated reflexes (two), clonus (one) and sensory changes (one). There

were two well defined relapses in each case in which retention of urine, requiring tidal drainage, was a distressing feature. Lymphadenopathy occurred in one case. In both, emotional lability was noted. Repeated examination of the cerebrospinal fluid revealed no abnormality. Virological studies were incomplete.

Galpine and Brady[32] reported seven cases which arose sporadically in the Coventry area in the late summer and fall of 1956, three years after the outbreak in their nursing staff. Four patients were female and three male. The early symptoms (sore throat, lassitude, drowsiness, vomiting, nuchal pain, backache, giddiness and headache) were similar to those reported elsewhere. Paresis was found in all cases and tended to fluctuate and shift. It was usually accompanied by aching, parenthesias and tenderness. Alterations in tone were rare, but twitching, cramps, involuntary movements and tremors occurred. The reflexes were brisk and the plantar responses difficult to obtain. The sensory changes noted included hyperpathia, hypoasthesia, anesthesia and astereognosis. Difficulty in starting micturition occurred in three cases and incontinence in one other. Shotty lymph nodes were found in the posterior triangle of the neck in three. Of six patients who were examined three months after their discharge from the hospital, two had recovered completely. The remainder complained of myalgia, weakness, parenthesias and diminished metal grasp. Examination of the feces in three cases failed to show any evidence of a cytopathogenic agent, and serological tests for poliomyelitis were negative.

In a second paper, Ramsay[31] reviewed his experience with thirty-four patients admitted from northwest London between April 1955 and December 1957. Headache was an almost universal symptom, and pain in the limbs, giddiness and pain in the neck occurred in about half of the patients. Lassitude, subjective sensory phenomena and back pain occurred in about a third, and sore throat, earache and cramps were less frequent. On general examination conjunctivitis and evidence of an upper respiratory infection were noted in one-third, and enlarged lymph nodes in one-fourth of the patients. In the nervous system, definite evidence of paralysis occurred in 50 per cent. Exaggerated deep reflexes, sensory disturbances and muscular tenderness were also prominent. Nystagmus and extensor plantar responses were found in about one-fifth. Cranial nerve lesions, tremors and myoclonus occurred in four patients. Low pyrexia was the rule. Results of serological tests for lymphocytic horiomeningitis, mumps, leptospirosis and poliomyelitis were negative in each case. Throat washings and feces were also examined.

Other Unexplained Outbreaks. Other problematic outbreaks have been described which share some of the characteristics already outlined. Bond[34] mentions briefly an outbreak of 463 cases in Tallahassee, Florida, in the fall of 1954. The disease, which was selective for married white women, was characterized by disturbances of mood, transient paresis, parasthesias and relapses. This outbreak and that reported by Wallis[35–37] from Cumberland, England, are probably similar to those already described but sufficient data have not been published on which to base a definite opinion.

Rose[38] and Wright and Morley[39] have reported epidemics of obscure encephalitis in West Africa, and have referred in their discussions to the outbreaks already described. In the former, which occurred in Sierra Leone, the onset resembled cholera with high pyrexia and prostrating diarrhea and vomiting, and the course was fulminating with terror, severe myalgia and vertigo. Pains around the costal margin similar to those of Bornholm disease were a common feature. A little less than one-third of the patients died. The cerebrospinal fluid was normal.

The outbreak in Nigeria, described by Wright and Morley[39], was characterized by low fever, tremor, aphasia, a normal cerebrospinal fluid and a favorable outcome in all cases. Certain of the epidemiologic features suggested an intoxication.

Other than an unknown etiology, the predilection of the agents for the nervous system, and a normal cerebrospinal fluid, neither of these outbreaks resemble those described in this paper.

McConnell[40] reported sixteen cases of illness among the student nurses of the University Hospital of Pennsylvania in 1945. Severe headache was invariable, hyperesthesia occurred in thirteen, meningism in twelve, and pleurodynia in ten. A diagnosis of epidemic pleurodynia (Borholm disease) was made, although the clinical picture was considered to be atypical. A low grade fever accompanied by "disproportionate severe generalized headache and myalgia" persisted for several weeds in five cases, and in two there were four and five relapses, respectively. Stupor and episodes of loss of consciousness occurred in one patient and sensory loss in another. The sequelae were headache, myalgia and pleuritis pain. Of five patients examined a mild pleocytosis was found in the cerebrospinal fluid in two. The similarities which this outbreak shares with the fourteen already described are obvious. However, in view of the absence of paresis, and the fact that the outbreak preceded the isolation of the Coxsackie viruses which could thus not be excluded in this instance, it has been classified separately.

Hook's[41] report from Hygiea, Sweden, underlines the horological difficulties in this field in the absence of pathological support. Under the title "Iceland disease'" he described four cases in the staff of a hospital in the summer of 1956. The affected persons, of whom two were physicians, worked in a "single room". (It is not clear whether this was a laboratory or a clinic.)

The first patient's illness developed gradually with mild muscular aches, parenthesias and weakness in the hands and feet. The paresis progressed over a period of several weeks and was accompanied by flaccidity and diminished reflexes. Mental depression was a feature in the later stages. Lumbar puncture in the second month of his illness revealed a protein of 60 mg. per cent, with a normal cell count. Electromyography showed the typical picture of reservation and a provisional diagnosis of infective polyneuritis was made. Polio and Coxsackie viruses were searched for without success. Vague illnesses characterized by headache and parenthesias subsequently developed in the patient's family.

The second patient's illness, which developed four weeks later, was acute. Three days after the onset of myalgia and parenthesias she had fever, indefinite stiffness of the neck and weakness of the legs. Within a further four days placid paralysis of the lower limbs was virtually complete. It had not regressed eight weeks later, and no fresh signs had developed. Lumbar puncture shortly after the onset showed 44 polymorphonuclear leukocytes, 52 lymphocytes and 90 r of protein. The suspicion that this case was, in fact, poliomyelitis is not dispelled by the failure to isolate polio virus from the stools in the fifth week, An unconvincing twofold rise in antibody titre against type 2 polio virus was demonstrated between the seventh and twenty-first day. The Coxsackie virus was not found. The third and fourth patients described by Hook suffered indefinite illnesses characterized by fatigue and parenthesias but exhibited no physical signs.

Hook's outbreak is difficult to classify. The localization of four cases to a small segment of a community suggests a common etiology. However, although the second case is clinically consistent with a diagnosis of poliomyelitis, the first with its slowly progressive paraplegia and sensory loss is not. The flaccidity of the paralysis, the failure to improve, and the electromyographic picture of reservation (Case 1) are features quite unlike the cases reported from Los Angeles, the Royal Free Hospital and elsewhere. Cases 111 and IV resemble the milder cases reported from these outbreaks. In our present state of ignorance it may be well to suspend judgment on this outbreak.

Laboratory Investigations

The Peripheral Blood. Examination of the cells of the peripheral blood has been on the whole unrewarding. Anemia has not been reported. In eight outbreaks[5,6,10,14,16–18] the total and differential white counts have been normal in most cases.

A special study of the leukocytes was made in the first Royal Free Hospital epidemic[12], a total of 750 specimens being examined from more than 400 confirmed or suspected cases. In addition, smears from 138 selected patients were examined by three independent observers. No specific changes were found. In about half the cases, relative lymphocytosis was seen during the early course of the illness. Occasional abnormal lymphocytes (Türk and plasma cell- like forms) were noted in some patients, but the changes characteristic of infectious mononucleosis did not occur. Similar findings have been reported in the endemic cases in the neighborhood of the Royal Free Hospital[29,31]. The authors stress the point that the changes are not specific and are identical to those seen in virus infections, such as poliomyelitis and the common cold. A relative lymphocytosis was also observed in one-third of the Bethesda cases. The small Berlin outbreak differed in that a polymorphonuclear leukocytosis occurred in all seven patients (range 9,700 to 15,300 cells per cu. mm.).

Information about the erythrocyte sedimentation rate is incomplete. In the Royal Free and Middlesex Hospital outbreaks it was normal. In the Alaska outbreak it was raised in the few patients in whom it was performed.

A positive agglutination reaction to washed sheep erythrocytes (Paul Bunnell test) is extremely uncommon[14] and when present further studies have suggested a remote infection.

The Cerebrospinal Fluid. The cerebrospinal fluid is known to have been examined in 199 cases in eleven outbreaks in which exact figures are available. The number of additional cases examined in the Durban and Alaska outbreaks is not recorded; lumbar punctures were not performed in the second Royal Free Hospital outbreak.

The cells: Normal cell counts (less than 15 cells per cu. mm.) have been the rule in all outbreaks except those in Iceland[6] and Alaska[17]. At Akureyri, two of five patients studied showed mild lymphocytosis, as did three others examined at Reykavik. In Alaska the total number of examinations is not stated but it appears that in two-thirds of those studied counts of 10 to 30 cells were found. In the remaining ten outbreaks in which exact figures are available, lumbar punctures were performed in 194 cases and less than 5 cells were observed in 180 of these (92.8 per cent). In the other fourteen cases (7.2 per cent) the cell counts ranged from 6 to 66 lymphocytes. In sporadic cases the results have been similar. Of twenty-seven cases studied, normal cell counts were found in twenty-five, a mild lymphocytosis in two.

Protein: Protein estimations were made in 194 cases in ten epidemics. In 182 cases (94.6 per cent) concentrations of 40 mg. percent or less were found, and in the remaining eleven (5.4 per cent) the readings varied from 48 to 85 mg.

per cent. In addition, we have the observation that in the Durban outbreak, abnormal concentrations of protein were "very rare". There is no information about the Alaska outbreak. Of twenty-seven sporadic cases examined, protein concentrations ranged between 50 to 80 mg. per cent in 4 cases; in the remainder the protein concentrations were less than 40 mg. per cent.

Apart from an occasional weakly positive Pandy test, no other abnormalities have been reported in the cerebrospinal fluid.

Creatinuria. White and Burtch[14] studied the excretion of creatine in thirteen patients. In twelve the urinary output was more than 100 mg. daily and in eight of these it exceeded 200 mg. It was considered that the findings could not be explained on the basis of physiological creatinuria as there were no athletes with exceptional muscular development in the group, and only one child. Creatine studies have not been reported by other workers.

Electromyography. Electromyographic studies were performing in two patients in the Copenhagen outbreak in 1952. Unfortunately, no description of the tracings is given. They were interpreted as showing "neurogenic weakness of peripheral or navicular origin". Macrae and Galpine[10] were the authors who first drew attention to a consistent electromyographic pattern in affected muscles on voluntary movement, which has subsequently been confirmed by Richardson[42] and Ramsay[31].
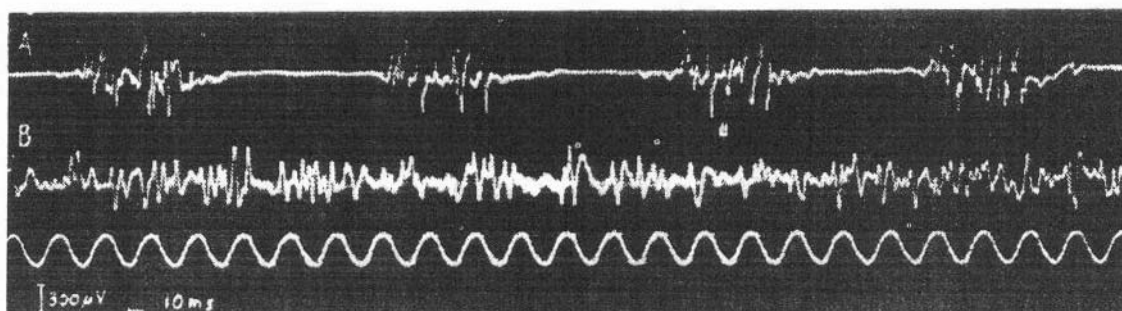
According to Richardson, who studied twenty-eight patients with marked motor involvement
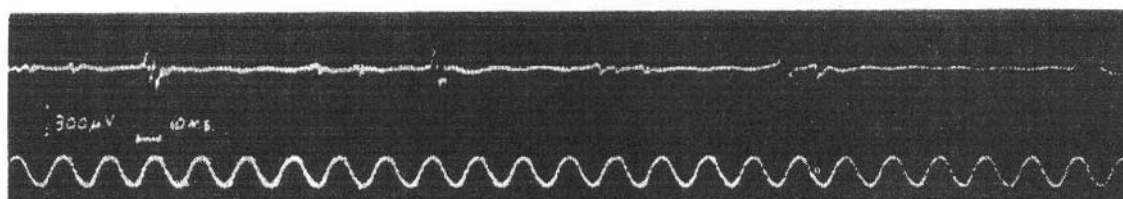
Recording from severely involved tibialis anterior muscle on maximal sustained volition. Recordings with concentric needle electrode and maximal sustained volition.

Figure 2B

Recordings with concentric needle electrode and maximal sustained volition. A, from weak tibialis anterior muscle. B, from normal contralateral tibialis anterior muscle. Calibration 50 cycles. 300 microvolts. (From Brit. M.J., 2:895, 1957.)

Figure 3
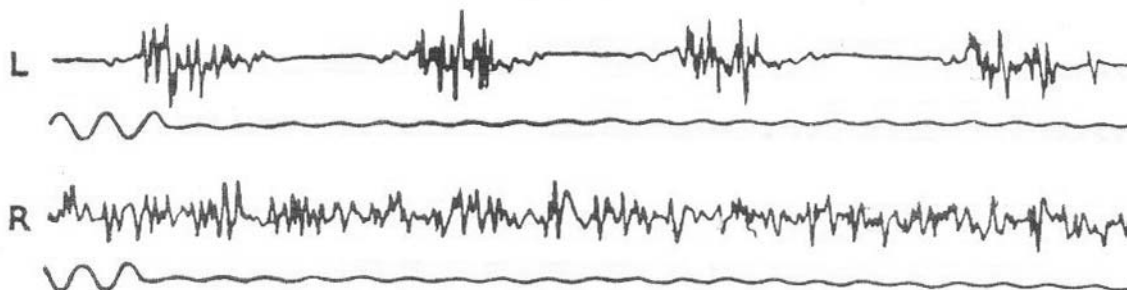
Electromyograms: upper register, from left (affected) tibialis anterior muscle on maximal volition, showing grouping of large polyphasic motor-unit potentials; lower register, from right (unaffected) tibialis anterior muscle on maximal volition, whowing complete interference pattern of normal motor-unit potentials. Calibration 500 and 100 μV at 50 cycles per second. (From Ramsay, A.M. Lancet, 2:1196, 1957.)

from the Royal Free Hospital outbreak, the strength–duration curves of the involved muscles were normal in all cases except one. Nerve conduction measurements cases were within normal limits. Evidence of lower motor neurone degeneration was therefore exceptional. Similar results were reported by Alexander[43] who performed nerve conduction studies on twenty patients from Durban.

Electromyography early in the disease revealed fasciculation potentials. With the onset of paresis an abnormality of recruitment occurred similar to that which has been described in involvement of the motor units at the level of the cord by Bauwens[44]. On volition, the number of motor unit potentials was severely reduced and in some instances the movement was initiated by prolonged polyphasic potentials. However, the accompanying

evidence of nerve fibre degeneration which might be expected in a protracted lesion of the motor neurone was not obtained.

During recovery, Richardson found changes similar to those described by Macrae and Galpine[10]. On volition the motor unit potentials were grouped in sequences lasting from 50 to 80 milliseconds, with regular intervals of complete inactivity giving rise to a tremulous contraction at a frequency of 5 to 10 per second. Ramsay and O'Sullivan[29] studied eight sporadic cases and reported singular findings. On electromyographic exploration of affected muscles, voluntary movement produced action potentials in groups of the same duration and frequency as those reported by Richardson. The similarity of the findings in the Royal Free Hospital cases and Ramsay's material is strikingly demonstrated in Figures 2 and 3. In

Table 2				
Attempts to Isolate Virus				
Location	No. of Cases Examined	Pathological Material Studied	Animal species	Tissue Culture Material
Los Angeles	0	Nil	Nil	Nil
Iceland	12	Blood, C.S.F., feces	Guinea pigs, hamsters, mice, suckling mice, monkeys	
Adelaide	5	Blood, C.S.F., throat washings, feces	Monkeys, suckling mice, weaned mice	Embryonated hen eggs
New York State	17	Feces, throat washings	Monkeys (2), suckling mice (15)	
Middlesex Hospital	3	Feces	Monkeys, suckling mice	Monkey kidney, monkey testicle
Copenhagen	0	Nil	Nil	Nil
Coventry Hospital	5	Feces	Guinea pigs (2), adult mice, suckling mice, monkeys (2), rabbit (1)	Human embryonic muscle and skin; monkey kidney, monkey testis
Bethesda Hospital	?	Blood, C.S.F., throat washings, feces	Suckling hamsters (9), adult mice (26), suckling mice (40)	Human HeLa(28), chorion (20), fibroblasts (10), monkey kidney (28), monkey testicle (31)
Seward, Alaska	0	Nil	Nil	Nil
Berlin	4	Feces	Inoculated into mice and tissue cultures were set up for Coxsackie and polio virus	
Durban Hospital	?		Extensive virologic studies negative	
Royal Free Hospital(1)	?	Blood clots, throat washings feces	Ferrets, guinea pigs, suckling hamsters, adult mice, suckling mice, monkeys	Fertile hen eggs, HeLa cells (9); human embryo brain (2), liver (1), spleen (1), kidney (6), human infant kidney (3), monkey kidney (10)
Punta Gorda	19	Blood clots, throat washings, feces	Suckling mice	HeLa, human liver, monkey kidney
Royal Free Hospital(2)	0	Nil	Nil	Nil

Note: Number of experiments, where given, indicated in parentheses. C.S.F. = cerebral spinal fluid.

his later review of thirty four cases, Ramsay[31] reported that twenty-one of twenty-six patients examined electromyographically (including the eight originally described) had shown the changes described. Galpine and Bradley[32], reporting seven sporadic cases from Coventry, found a reduction in the number of motor unit potentials and grouping in all five patients examined. Polyphasic and abnormally large potentials were also found.

Electroencephalography.

Electroencephalograms have been studied by Fog[9], Ramsey and O'Sullivan[29], Galpine and Brady[32] and Poskanzer et al.[16]. Some non-specific abnormalities were reported in patients with behaviour disorders by Ramsay and O'Sullivan. In all other cases the electroencephalogram has been normal.

Virology. In view of the dissimilarity of the clinical picture to any known bacterial infection, attention has naturally been focused on isolating a virus as the responsible agent. (Table 2). In nine of the fourteen outbreaks unsuccessful attempts were made to isolate the poliomyelitis and Coxsackie viruses. In the Middlesex Hospital outbreak[8] polio virus Type 3 was isolated from the feces of one case. However, in view of the failure to isolate any detectable antibody from serial specimens of this patient's serum the extremely unusual clinical picture (bilateral perceptive deafness developed), and a normal cerebrospinal fluid, it was concluded that this virus was probably not responsible for her illness. Table 2 shows that unsuccessful attempts have also been made to isolate other viruses in a number of outbreaks. Particularly extensive investigations were

carried out in the Bethesda and Royal Free Hospital epidemics.

In four outbreaks no attempts to isolate a virus were made; one of these was the small second Royal Free Hospital outbreak[13], which was regarded as clinically identical with the large epidemic which had been the subject of extremely extensive virologic studies the previous year. In the Seward outbreaks[17] the only investigation performed consisted in random serological studies in nineteen patients who were experiencing subacute symptoms, revealing that the "neutralization titres against the three types of poliomyelitis virus were generally low and showed no consistent pattern." In the Los Angeles[5] and Copenhagen[9] outbreaks no virological studies were made.

Serological studies (Table 3) have also been widely performed. Immune bodies to the mumps virus in titres suggesting remote infection were found in a few cases. In the Bethesda outbreaks thirteen serum pairs were examined for antibodies against polio virus. A questionable fourfold rise in the titre occurred in three cases, one against each of the three types of virus. Otherwise serological tests have been uniformly negative.

Bacterial Studies. In the Bethesda outbreak the prominence of diarrhea as an early symptom directed attention to the possibility of an enteric infection. Organisms of two strains of the Bethesda-Ballerup paracolon group were isolated from feces from twelve of thirty-eight nurses examined and from only one of fifty-four persons who were on the hospital staff at the time of the epidemic and remained well. H and O serum agglutinins against the Bethesda-

Table 3

	Los Angeles	Iceland	Adelaide	New York State	Middlesex Hospital	Copenhagen	Coventry Hospital
A.P.C. virus							
Brucellosis							
Coxsackie				0 (17)			
Encephalitis Eastern Equine	Nil	0 (12)				Nil	
Encephalitis Japanese B	Nil	0 (12)				Nil	
Encephalitis Western Equine		0 (12)					
Encephalitis St. Louis		0 (12)					
Encephalo-myocarditis			0 (5)				0 (10)
Herpes Simplex							
Influenza A		0 (12)					
Influenza B							
Influenza C							
Leptospirosis			0 (5)		0 (8)		0 (10)
Louping Ill							
Lymphocytic Choriomeningitis		0 (12)	0 (5)		0 (8)		0 (10)
Mumps			0 (5)		* (8)		* (10)
Paracolon (Bethesda-Ballerup)							
Polio Virus			0 (5)	0 (17)	3† (10)		0 (10)
Psittacosis							
Q. Fever		0 (12)					
Rabies		0 (12)					
Rickettsia Burneti							
Toxoplasmosis							

	Bethesda Hospital	Seward, Alaska	Berlin	Durban Hospital	Royal Free Hospital (1)	Punta Gorda	Royal Free Hospital (2)
A.P.C. virus	0 (7)				0 (?)		
Brucellosis	† (13)		0 (7)			0 (12)	
Coxsackie	0 (5)						
Encephalitis Eastern Equine				No		0 (12)	
Encephalitis Japanese B				details			Nil
Encephalitis Western Equine				known		0 (12)	
Encephalitis St. Louis						0 (12)	
Encephalo-myocarditis					0 (6)		
Herpes Simplex					0 (?)		
Influenza A			0 (7)		0 (?)		
Influenza B			0 (7)		0 (?)		
Influenza C					0 (?)		
Leptospirosis					0 (?)	0 (12)	
Louping Ill					0 (?)		
Lymphocytic Choriomeningitis						0 (12)	
Mumps					0 (?)	* (12)	
Paracolon (Bethesda-Ballerup)	See text					0 (12)	
Polio Virus		† (19)					
Psittacosis					0 (?)		
Q. Fever							
Rabies							
Rickettsia Burneti					0 (?)		
Toxoplasmosis					0 (?)		

Note: Figures indicate number of positive tests; in parentheses, number of cases studied. * Immune bodies in titres suggesting remote infection found in some cases. † The findings were of doubtful significance and are discussed in the text.

Ballerup group (at a titre of 1:40 or more) were found in twenty-two of forty-seven affected nurses and in three of twenty-seven control subjects. In eleven affected nurses a rise and fall in titre was demonstrated during the period of observation. A kitchen girl who had started work one week before the onset of the epidemic was the only person in the entire study who showed both serological strains of organism in her stools. Examination of sixty asymptomatic nurses three to seven months after the end of the epidemic revealed antibody titres in two cases, but no positive cultures.

There is thus strong circumstantial evidence to suggest that. the Bethesda-Ballerup paracolon organisms were related to the epidemic of clinical illness among the nursing staff. However in the absence of other evidence (1) that a disease can be transmitted by these organisms either in man or in animals, (2) or that they produce a neurotoxin, it is premature to conclude that they caused the epidemic. As Sheldon and his colleagues have themselves suggested, the findings may indicate simply that fecal contamination of food was occurring in the hospital kitchen at the time of the epidemic. It is possible that an unknown causative organism was being spread in addition to the Bethesda-Ballerup organism.

It is important to note that attempts to isolate paracolon organisms from patients during the Punta Gorda outbreak were unsuccessfull[16].

Poisons. In view of the apparent predilection for hospital staffs, the question has arisen whether or not the disorder may be due to an occupational toxic hazard. This possibility received particular attention in the Royal Free Hospital outbreak[27]. Insecticides, paints and detergents received scrutiny, with negative results. Similar studies were negative in the Durban outbreak[18] and at Bethesda[15].

The Case for a Clinical Entity

It is significant that the first review of the syndrome under discussion was entitled, "Not poliomyelitis"[45]; the second, "A new clinical entity?"[22]. In later articles entitled, "Epidemic myalgic encephalomyelitis"[46], "Benign myalgic encephalomyelitis"[46a] and "Epidemic neuromyasthenia"[15,16], the authors considered themselves on sufficiently strong ground to describe and name the syndrome. This sequence indicates that the first and minimum requirement in the definition of an entity is the essentially negative one of showing that the syndrome is not an unusual manifestation of a disease already recognized. Later, as evidence accumulates, it may be possible to define the disorder in positive terms.

Poliomyelitis. In nine outbreaks an initial diagnosis of poliomyelitis was made. In favor of this diagnosis were the mode of onset in many cases (headache, pain in the neck and myalgia), the development of paresis and the season of the year. The low or absent fever, so unusual in poliomyelitis at the beginning of the paretic phase, and the rarity of a diphasic illness were at first discounted. However, other atypical features made their appearance in the later stages of the illness in such frequency that the diagnosis of poliomyelitis was withdrawn. In the second and third weeks the distinguishing features were (1) a longer active course with the development of fresh neurological symptoms and signs later than

occurs in poliomyelitis, (2) the prominence and persistence of sensory phenomena, (3) the retention or exaggeration of deep reflexes in the paralyzed limbs, and (4) the normal cerebrospinal fluid in most cases.

In some outbreaks the persistence of muscular pain after the development of paresis, the occurrence of tremors and involuntary movements and the high incidence of retention of urine in the absence of' severe paralysis were further points against the diagnosis of poliomyelitis at this stage.

The subsequent subacute and chronic course of the disorder, with its mental symptoms and partial or complete remissions and exacerbations, is quite distinct from poliomyelitis which runs its active course within a week of the onset of the major illness. With the exception of the Iceland epidemic, muscular wasting in patients with persistent paralysis has been extremely rare and in such patients no electromyographic evidence of denervation has been found. The over-all mortality in more than 1,000 cases has been nil. From the clinical point of view, the differences from poliomyelitis become progressively clearer as the illness develops.

Epidemiologically, the high attack rates (Table 1) and the predilection of the disorder for small semi- closed communities are also against the diagnosis of poliomyelitis.

The final evidence lies in the laboratory findings. In spite of careful search in ten of fourteen outbreaks, poliomyelitis virus was found in only one case[8] and in this patient no detectable antibodies appeared in the blood.

Other Enteric Viruses. There is now good evidence that enteric viruses of thc Coxsackie group[49] cause epidemic pleurodynia[50] and encephalomyocarditis in babies[51]. Viruses of the Coxsackie and Echo groups have also been recovered from cases of aseptic meningitis[52] and lower motor neurone type paralysis.

Scrutiny of reports claiming that they have been concerned in outbreaks of encephalitis in adults shows that objective evidence of damage to the central nervous system has, in fact, been the exception rather than the rule[53,54].

In the outbreaks reported here certain clinical similarities with epidermic pleurodynia, notably the occurrence of pleuritis chest pain in six outbreaks, of abdominal pain in six, and pain in the shoulders in twelve, stimulated a search for these viruses. In nine outbreaks material was injected into suckling mice with negative results (Tab1e2); and in five instances[8,10,12,15,16] tissue cultures of kidney cells from monkeys failed to grow ECHO viruses. In other respects, notably the mental symptoms and the chronicity of some cases, the outbreaks reported here are unlike any that have been found to be associated with Coxsackie or Echo viruses.

Encephalitis Lethargies. The occurrence of tremors, myoclonus or other involuntary movements in a few cases in seven outbreaks raised the question of the reappearance of encephalitis lethargies in epidemic form. Although this disease was notably pleomorphic[55], it has certain distinct clinical and epidemiologic features, which are not shared by any of the outbreaks reported here. According to Von Economo[55] it occurred

chiefly in the first three months of the year, was of low infectivity, with no sex predominance and a high mortality. Postencephalitic Parkinsonism occurred in about 30 per cent of all recognized cases. This complication has not been recorded in the illness described here, although one Royal Free Hospital patient had choreoathetoid movements of the right arm with cog-wheel rigidity some months after the acute illness. Involuntary movements have also been reported in the chronic stage in a few of the Alaskan cases[17]. Delinquent behavior, such as occurred after encephalitis lethargies epidemics, has not been described.

The Arthropod-Borne Encephalitides. The various arthropod-borne encephalitides have common epidemiological and clinical features which distinguish them from the syndrome reported here. As might be expected, these diseases occur most frequently in field and forest workers who are exposed to the bites of mosquitoes, ticks and bird and animal parasites[56], and evidence of spread by personal contact is uncommon. The various types of insect-borne encephalitis share an acute onset with high fever and headache, followed in severe cases by delirium, convulsions, tremors and spastic paralyses. Death occurs within ten days in a variable proportion. A pleocytosis of 100 to 500 cells in the cerebrospinal fluid and a polymorphonuclear leukosytosis in the peripheral blood are characteristic.

The syndrome described in this paper, with its institutional outbreaks, evidence of spread by personal contact[5,6,12], absence of delirium or convulsions, predominantly normal cerebrospinal fluid and absent mortality, is in striking contrast. From the virological point of view, the agents of the insect-borne encephalitides are best recovered from nervous tissue which was not obtained from this material. However, a search for antibodies against some of the known types of encephalitis virus was made in the Iceland and Punta Gorda[16] outbreaks and against louping ill (Russian spring-summer encephalomyelitis in the Royal Free Hospital cases[12] without success.

Infectious Mononucleosis. A diagnosis of infectious mononucleosis was seriously entertained at the onset of the Royal Free Hospital outbreaks. In favor were the known predilection of this disease for hospital staffs, the lymphadenopathy, and the presence of a few atypical lymphocytes in the peripheral blood in some cases. A wide variety of neurological manifestations have been described in infectious mononucleosis, but these are rare. As the epidemic developed, the overwhelming frequency of neurological symptoms and signs made this diagnosis unlikely, and the failure to demonstrate typical Downey cells or significant titres of heterophile antibodies finally excluded it.

Other Infections. Searches for a wide variety of other agents have been carried out (Tables 2 and 3) without success.

The Question of Hysteria. The question of hysteria has been raised in five outbreaks[5,6,9,12,20] and by Galpine and Brady[32] and Ramsay[31] in the discussion of their endemic cases. Most authors agree that hysterical manifestations have occurred in a few patients[5,9,31], particularly in the later

stages[12], but none has felt that it has contributed significantly to the pattern of the disease.

In an illness in which there has been a selectivity for young women, no mortality, and few positive laboratory findings, it is important to examine the possibility that hysteria may have accounted for part or all of the clinical picture more closely. Epidemic hysteria has been recognized for many centuries as a particular hazard in institutions containing women[58]. It has presented in many bizarre ways from the mass compulsive dancing (St. Vitus Dance) of the middle ages, to the "quaking" of the early Quakers, the fits of Wesley's converts and the effort syndrome of soldiers in the 1914–1918 World War. The form and content of the manifestations depend upon the ideas and fears of the age[59].

No one can seriously contend that every patient in all the outbreaks described in this paper has been hysterical. The presence of definite ocular, facial and palatal pareses, or nystagmus, and of extensor plantar responses in rare instances, and a definite pleocytosis in the cerebrospinal fluid in a few cases indicate organic disease of the nervous system in a minority at least, unless we are to doubt the competence of a number of different observers.

A more reasonable viewpoint would be that the majority of the cases constitute a hysterical reaction to a small number of cases of infection of the nervous system, for example, poliomyelitis. Thus it will be readily admitted that an epidemic of poliomyelitis, such as occurred in Los Angeles in 1934, would produce overwork and emotional strain in the nursing staff of the hospital concerned. Many of the nurses would naturally feel apprehensive about becoming ill with the disease, and might be inclined to misinterpret the minor aches and pains of every day life. With the development of a few genuine cases of poliomyelitis among the staff and the resulting increasing tension, it is possible to envisage an epidemic of hysterical paralysis.

An attractive case could be made for such a hypotheses. The high attack rates in the most suggestive groups of the community, the predilection for hospital staffs and the association with preceding or concurrent outbreaks of poliomyelitis might thus be explained. Clinically, the absent or insignificant fever, the preeminence of sensory phenomena, which are admittedly often of bizarre distribution and content[13,15], the fluctuation of symptoms and signs from day to day, and the high incidence of negative cerebrospinal fluid findings would also fit in with this hypothesis. Further support might be obtained from the peculiar nature of the paresis. Paralysis without the disappearance of tone and deep reflexes and subsequent atrophy on the one hand, or true spasticity and extensor plantor responses on the other is suspicious of hysteria. As Brain[60] has pointed out, inability of the patient to relax the affected limb in such cases may cause the deep reflexes to appear exaggerated. Tremors on volition and involuntary movements may also be present in such patients. A jerky contraction against resistance is often prominent[60]. If we add muscle pain and tenderness, which are admittedly uncommon in hysterical paralysis, such a description resembles closely the features of the paralysis in the Royal Free

Hospital cases[12] which were attributed to a deep subcorticol lesion, and is similar to those described in many less detailed reports.

There are also strong arguments against the idea that the syndrome constitutes a mass hysterical reaction to a few cases of poliomyelitis. In the first place, in the minority who had undoubted objective physical signs, the clinical picture was quite unlike poliomyelitis. In this minority, nystagmus[7,8,9,12,18,19], ophthalmoplegia[8,12], facial palsy[5,7,9,12,18,19], palatal paresis[5,8,12] and extensor plantor responses[8,9,12] were recorded, but true placid paralysis with absent reflexes did not occur, and subsequent atrophy was recorded with any frequency in only one outbreak[6] and in exceptional instances in two others[5,12]. In addition, these patients shared the other characteristic features, namely myalgia, sensory changes, low pyrexia, mental symptoms, and a chronic or relapsing course, which were experienced by the majority of patients who had no truly objective physical signs. Thus we would be forced to the conclusion, on this hypothesis, that even the patients with objective findings were also suffering from hysteria. This seems unlikely.

In the second place, the relationship to poliomyelitis is not constant. At the Royal Free Hospital no patient with poliomyelitis had been admitted to the hospital prior to the outbreak, nor was the diagnosis entertained in the initial cases. There was no undue apprehension about poliomyelitis among this hospital staff, but rather about infectious mononucleosis which was the early diagnosis. In spite of this the course of the disease and the type of neurological involvement was similar to that found in Los Angeles. In the Coventry outbreak six of the twelve patients had been nursing poliomyelitis cases for several years, and it is difficult to imagine why such experienced persons should suddenly manifest a hysterical reaction to the fear of this disease. In the Middlesex Hospital, Berlin and Bethesda cases there was no known contact with poliomyelitis and in the early cases at least, no reason for anxiety about it in the communities concerned.

The mental symptoms which are a constant feature of all the outbreaks are not typical of hysteria. Disorders of consciousness and convulsions such as may be seen in hysteria have been extremely rare. A single grand mal seizure was reported in a small child in Alaska. Shallowness of affect and "belle indifference" have not been seen. On the contrary, depression and undue emotional lability have been the rule. In the acute stage, terrifying dreams, panic states, uncontrollable weeping and hypersomnia occur. In the convalescent stage the prominent features are impairment of memory, difficulty in concentration and depression. These symptoms are more consistent with cerebral damage than with hysteria. Many years ago Von Economo[55] stressed the ease with which the mental symptoms of encephalitis may be confused with those of psychoneurosis. The slight lymphocytosis in the cerebrospinal fluid in two outbreaks[6,17] which shared many other features with the remainder, and the presence of a characteristic electromyogram in cases from three separate localities are further strong arguments in favour of an organic etiology.

Final points against mass hysteria as a major factor in the syndrome are the consistency of the course of the illness, and the similarities in the symptoms described, in spite of a wide variation in the types of community affected, from hospital staffs on the one hand to semi-rural and urban populations on the other. The fact remains that in sporadic cases the illness may be extremely difficult to differentiate from hysteria and other types of psychoneurosis[31]. The diagnosis should therefore be reserved, in isolated instances, for patients with evidence of acute damage to the brain or cord, including the characteristic paresis. If not, the syndrome will become a convenient dumping ground for non-specific illnesses characterized by fluctuating aches and pains, fatigue and depression.

The Homogeneity of the Material. The clinical and epidemiologic evidence suggests that the fourteen outbreaks described in this review have not been due to any known heliotropic infection. The virility evidence supports this contention so far as it goes, but it is incomplete. Thus poliomyelitis and Coxsackie virus were not formally ruled out in four outbreaks, and Echo viruses were not excluded in nine. It might be argued that at least some of the apparent clinical similarities are due to unconscious bias or undue emphasis on the part of observers familiar with the features of previous epidemics. Such bias cannot have contributed towards the striking reported similarities between the Los Angeles and Royal Free Hospital outbreaks[5,12] because Gilliam's paper was unknown to the British authors. These similarities are evermore impressive when it is appreciated that bias was probably operating in opposite directions. In the Los Angeles outbreak the initial diagnosis was poliomyelitis, and the patients were cared for by orthopedists; in the Royal Free Hospital cases the initial diagnosis was infectious mononucleosis and patients were treated by internists and neurologists. Further independent evidence is supplied by the Copenhagen cases. Fog's paper[9] was not known to the authors of the later Middlesex, Durban, and Royal Free Hospital reports, although once again they share many common features. It seems therefore that the syndrome is not a self-perpetuating medical artefact.

There are also important differences between the outbreaks. The paralysis rate varies from 10 per cent in the Punta Gorda outbreak to 80 per cent in the Los Angeles cases. The Los Angeles, Middlesex, Durban and Royal Free Hospital epidemics differ quantitatively from the remainder in regard to the frequency of neurological signs (other than paresis), notably cranial nerve lesions hyperpathia and retention of urine. They share with the Copenhagen cases a high incidence of parenthesias. On the other hand the Royal Free Hospital epidemics stand apart from the remainder because of the very high incidence of lymphadenopathy, which was otherwise limited to a few cases in the New York State, Middlesex[8(c)] and Durban outbreaks. The Iceland and Alaska epidemics differ from the rest in that a slight lymphocytosis in the cerebrospinal fluid was the rule rather than the exception. The length of the illness and the incidence of subacute and chronic cases have also varied.

Two outbreaks in particular stand apart in several important respects from the rest and it is debatable whether or not they should be classified with them. In the small Berlin

outbreak[15] the illness was brief, sensory symptoms and signs were absent, and there were no sequelae or chronic cases. A leukocytosis in the peripheral blood was another distinguishing feature. The onset was November, later than in any other outbreak in the Northern Hemisphere. The outbreak at Punta Gorda[16] also began at an unusual time of the year (February). The onset of symptoms was insidious in all cases. Most of the cases were diagnosed on the basis of a house to house survey, presumably by retrospective questioning. Paresis was exceptional, and other objective evidence of disease of the nervous system was extremely uncommon.

In mild cases, when paresis and other signs of neurological involvement are absent, the illness has few differences in its early stages from many short-lived infections characterized by headache and generalized aches. Even in these patients, however, the degree of malaise and the severity of the pains are disproportionate to the disturbances of temperature and pulse. In the convalescent stage in such cases the easy fatiguability, the aches and pains, and the emotional disturbances without definite physical signs lead to difficulty in differentiation from psychoneurosis. Indeed, in the absence of an epidemic such a differentiation may be impossible.

In its epidemic form the illness is distinctive and therefore has a rightful place in medical literature as a clinical entity. Its epidemiological features suggest that it may be an infection. However, in the absence of any pathological evidence it remains uncertain whether it is due to a single agent or to a group of related agents.

As far as sporadic cases are concerned the diagnosis can be made with a degree of certainty only in cases which show all or nearly all the characteristics herein described including paresis and some other objective evidence of neurological involvement which cannot be simulated. Negative virologic studies are also desirable. The diagnosis of less severe sporadic cases must await further knowledge of the pathology and the development of an objective laboratory test. Although further work is required before the electromyographic changes can be regarded as diagnostic, they may provide objective evidence of disease when this is otherwise lacking.

Treatment. No specific treatment is known to affect the course of the disease. Antibiotics were tried in the early stages of the Bethesda outbreak, when the diagnosis was uncertain, and in those patients in the Royal Free Hospital who had complicating intercurrent bacterial infections. No beneficial effect on the basic disease was observed. Steroid therapy has not been tried.

The importance of rest as early in the disease as possible and as absolute as practicable is stressed by many authors[5,12,15,18,19]. Paretic limbs should be immobilized in the correct posture. Local heat may be used to abate pain and spasm. The association of premature rehabilitation with relapse is well described[5,12,18,19] and it is probable that bedrest should be maintained for some time after the disappearance of symptoms.

Symptomatic treatment is important in this painful and protracted disorder. Muscle relaxants such as meprobamate* have been

tried[12,15,17] and have relieved muscle pain and tenderness in some cases. The sedative action may also be of value[17].

In a few cases full doses of narcotics may be necessary to control pain[5,8,12].

Complications should be treated as they arise. Retention of urine can usually be controlled by parasympathomimetic drugs such as carbachol[12] but occasionally catheterization even tidal drainage will become necessary[12]. In rare instances of bulbar palsy, tube feeding has been necessary[12]. An artificial respirator has been required for a short time in three cases[5,8]. Shock treatment for severe depression was required in three of the Royal Free Hospital patients[12].

In the subacute and chronic stages constant encouragement and support is essential. The patient may be reassured that the trend is toward improvement and final recovery. Rehabilitation should be conservative and return to work gradual.

Nomenclature

The wisdom of naming a disorder, the nature of which cannot at present be proved, and which may be due to more than one agent, is debatable. That there are successful precedents is shown by the history of epidemic pleurodynia[24,25,50] and herpangina[4,61], both of which have subsequently proved to be virologic entities. In view of the widespread agreement that the illness described here is clinically recognizable in its own right, at least in severe cases[15,17,22,31,46], various authors have been of the opinion that a name is necessary for reference purposes. Unfortunately there has been no agreement as to what this name should be. White and Burtch[14] suggested "Iceland disease". This has the disadvantage of all eponyms that it gives no inkling to the uninformed of the nature of the disorder. It is also incorrect on historical grounds as the Los Angeles Outbreak described by Gilliam is the original account in the literature. The same disadvantages (with the added difficulty of pronunciation) apply to "Akureyri disease" which is preferred by Sigurdsson and Gudmundsson[21].

The first attempt at a descriptive name was made by Fog[9] who suggested "neuritis vegetativa" in the belief that the autonomic nervous system bore the brunt of the damage. A further suggestion was made in an editorial in the Lancet in 1956[22]. It was hoped that the term "benign myalgic encephalomyelitis" would emphasize the absent mortality, the severe muscular pains, the evidence of parenchymal damage to the nervous system, and the presumed inflammatory nature of the disorder. This term has been adopted by Galpine and Brady[32] and Deisher[17] in subsequent articles. It has also been criticized by Sigurdsson[62] and the staff of the Royal Free Hospital[12,27]. Sigurdsson objects that the disease is not always benign, not invariably myalgic, and possibly never encephalomyelitis. Benignity is relative; it seems that "benign" is justified by the fact that there is no other recorded infective disease of the central nervous system without mortality. As various authors have stressed[5,8,12], the pain in this disease, although not invariably present, may be devastating, and is perhaps the feature which impresses itself most forcefully on the

observer. As far as the final term is concerned, the clinical impression that the lesion is central rather than peripheral is supported by the electromyogram. In our present state of ignorance "encephalomyelitis" seems preferable to "encephalopathy" because it conveys the suggestion that the disease is infective in origin, which is almost certainly the case.

In the Royal Free Hospital report it is pointed out that the name fails to describe the involvement of the lymph nodes and liver. As the author has indicated elsewhere[63], a fully descriptive name such as "benign ameningitic myalgic lymphoreticular encephalomyelopathy" if impracticable. Shelokov et al.[15] and Poskanzer et al.[16] have coined the phrase "epidemic neuromyasthenia". The first term is misleading because it suggests that the disorder is confined to epidemics, the second (translated nerve-muscle-weakness) is either meaningless or, if it means anything, suggests a disorder of the muscle end-plate, which is contrary to the electromyographic evidence. The verbal similarity with "neurasthenia" (i.e., psychoneurosis) is particularly unfortunate.

It is unlikely that an adequate term will be found until fresh evidence is available. In the meantime "benign myalgic encephalomyelitis" may act provisionally as a rallying point in the current list of medical literature for patients with the clinical features already described.

Summary and Conclusions

Fourteen outbreaks of a paralytic illness of worldwide distribution are described. Twelve of these have so many epidemiologic and clinical features in common that there is a prima facie case for a single or related group of causative agents.

The epidemiologic features are a high attack rate as compared with poliomyelitis, a predilection for residential communities, a higher attack rate in women than in men, a tendency to occur more commonly in young adults, and the commencement of most outbreaks in the summer months. The evidence is consistent with the hypothesis that the disorder is an infection which is spread by personal contact.

The fact that hospital staffs, particularly nurses, have borne the brunt of seven outbreaks suggests an occupational hazard. An alternative explanation is that the unusual nature of the illness has been noted in such persons because of a higher standard of diagnostic skill at their disposal than is available to the members of other residential communities.

Severely affected patients show a characteristic clinical picture. After an acute or subacute onset with headache, symptoms of a gastro-intestinal or upper respiratory upset, muscular pains and low or absent fever, an unusual type of paresis develops which is rarely associated with the classic signs of lower motor neurone or pyramidal tract involvement. This is often accompanied by parenthesias, sometimes by sensory loss, and occasionally by painful muscular spasms, myoclonus or other types of involuntary movement. As the paresis recovers a curious jerky muscular contraction on volition has been noted in some instances.

Involvement of the cranial nerves and the bladder may occur.

Convalescence has been prolonged by fatigue and recurring myalgia but recovery has usually been complete within three months. In a proportion which varies from outbreak to outbreak a well defined state of chronic ill health has developed, characterized by fluctuating myalgia and paresis, partial remissions and exacerbations, and depression, emotional lability and lack of concentration. The major differences within the group of outbreaks lie in the incidence of lymphadenopathy, paresis, and mild lymphocytosis in the cerebrospinal fluid.

Clinical laboratory studies have on the whole proved unhelpful. With the exception of two outbreaks in which a mild lymphocytosis was found, the cerebrospinal fluid has been normal in 95 per cent of cases investigated. An unusual electromyogram has been found in two outbreaks and in some sporadic cases.

No deaths directly attributable to the disease have occurred and the pathology remains unknown. In spite of the sidest investigations, no known bacterial or viral pathogen has been incriminated. In particular, there is no evidence that the poliomyelitis Coxsackie or Echo groups of viruses have been responsible.

Evidence is adduced to show that the outbreaks can be distinguished on clinical grounds from poliomyelitis, encephalitis lethargica, the arthropod-borne encephalitides, epidemic myalgia and infectious mononucleosis. The disorder is not a manifestation of mass hysteria.

It is concluded that the disease is recognizable in its epidemic form on clinical and epidemiologic grounds and therefore may properly be considered a clinical entity. In its sporadic form, which is now well documented, the diagnosis should be reserved at present for severe cases with definite neurological signs including paresis and the characteristic fluctuating course. The disease is probably due to infection by an unknown agent or group of related agents.

The problems of nomenclature and treatment are also discussed.

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Sir (Ernest) Donald Acheson, KBE 1986

Sir (Ernest) Donald Acheson, KBE 1986, has just retired after holding the post of Chief Medical Officer, Departments of Health and Social Security for Great Britain. It is of notable interest that this principal early M.E./CFS researcher had risen to become the chief Medical Officer for Great Britain. Dr. Donald Henderson, one of the early American M.E./CFS pioneers whose work is also in this book, went on to become Dean of Medicine of Johns Hopkins and is presently the White House Chief of Science for the U.S.A. After Sir Donald Acheson graduated from Oxford in 1946 he held numerous senior positions, including Professor of Clinical Epidemiology, University of Southampton, Chairman of Slow Virus Group, Visiting Professor, McMaster University, Canada 1977. He has also held numerous important posts in many universities in the United Kingdom and New Zealand. *The information about Sir Atheson was obtained from the British **Who's Who 1992**, Collier Mcmillian Press, Cambridge, Ontario.*