A 30-Year Historic Review of a Community Hospital Epidemic Outbreak Characterized by Venous Inflammation, Severe Pain, and Long-Term Disability

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ABSTRACT

Background. A 1975 outbreak, characterized by severe venous involvement, affected nurses and staff of a California community hospital spreading to other health care workers and unrelated persons. Spread from epidemic to quintary cases was noted. The purpose of this report is to delineate the hallmark symptoms of the outbreak and determine the functional state of affected patients 30 years later.

Methods. Sixty-one hospital epidemic cases were reviewed, and 30-year follow-up assessed by questionnaire, interview, and physical examination.

Results. Painful veins; flu-like symptoms; and severe generalized pain, exhaustion, weakness, cognitive disturbances, and nervous system abnormalities marked the outbreak. In 2006, 30 patients were available for follow-up, 14 were deceased, and 17 were lost to follow-up. Of the living, 29 never became well citing generalized pain; energy absence; confusion, memory loss, other neurologic problems; and leg discomfort. Only eight were able to return to work, five of who functioned with difficulty. Of those deceased, 11 never worked after onset.

Conclusions. A severe viral-like epidemic, apparently communicable and carried latently with pronounced venous inflammation resulted in permanent disability in 75% of those surveyed 30 years later.
INTRODUCTION

An infectious epidemic outbreak, characterized by acute onset of severe influenza-like symptoms and accompanied by severe venous involvement, occurred in 1975 in a community hospital in Carmichael, a suburb of Sacramento, CA. Vascular features ranged from spontaneous bruising with numbness, tingling, and burning to painfully swollen veins. The severity of disease appeared to be associated with the extent of vascular sequelae. The hallmark symptom of painful veins appeared to be similar but more severe and extensive than the Epidemic Phlebodynia documented in three other hospital epidemics reported in 1953, 1957, and 1965 (1-3). Headaches, sore throat, fever, dizziness, runny nose, nausea and vomiting, severe exhaustion and weakness, severe generalized pain, disturbances of cognition/mentation, and nervous system abnormalities resembled Epidemic Neuromyasthenia (ENM), Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME). Today these illnesses are thought to represent the same and/or a spectrum of related disease states.

The first two cases appeared in February. Most occurred between July and November, and several cases tailed out to 1978. After the initial flu state, patients had a constant plateau of illness punctuated by unpredictable relapses, often worse than the initial illness. The epidemic spread to all departments of the Hospital, and the outbreak was equally severe. It first affected Intensive Care Unit nurses and staff and spread to other healthcare workers, their families and unrelated persons. The outbreak was reported to the California State Department of Health with subsequent investigation by the Centers for Disease Control and Prevention (CDC).
The purpose of this report is fourfold: (1) to report the initial investigative epidemiology findings of the CDC; (2) to describe the 1975 hospital outbreak, present a representative patient to highlight the scope of the illness, and report 30-year follow-up; (3) to delineate the unusual vascular abnormalities associated with the outbreak; and (4) to discuss this outbreak and illness in context to other associated diseases.
METHODS

Institutional Review Board or Ethics Committee approval was not required for the data collection and analysis of the presented hospital outbreak. The principal investigator of the outbreak was asked by the hospital to see and manage all the infected patients, and all patients requested that he continue as their treating physician. Verbal consent and signed written letters of understanding/consent to permit use of their medical information and photographs for publications and presentations were obtained from all patients reported herein. Since HIPPA privacy and other confidentiality concerns were not codified into federal regulations at the time of outbreak data collection, a HIPPA Privacy Officer was consulted to insure patient anonymity.

At the time of the outbreak the author was affiliated with the University of California Davis and was a staff Infectious Disease Specialist at Mercy San Juan Hospital in Carmichael, California. He was appointed chairman of the hospital committee to investigate the outbreak and also served as the attending physician for the patients presented in the review of the 1975 epidemic cases and those in the 30-year follow-up case study.

An epidemic intelligence officer from the Hospital Infections Branch, Bacterial Diseases Division, Bureau of Epidemiology of the Center for Disease Control was contacted by the Sacramento California Health Department to formally investigate the outbreak. A case definition was originally devised for presumed thrombophlebitis (inflammation of the veins with blood clot formation which produces pain, skin redness, and swelling) and then extended to include inflamed superficial and deep veins for secondary and sporadic cases (Table 1). A non-symptomatic control group
that included ICU and staff nurses, family contacts, and non-hospital contacts was generated by the California State Health Department and subsequently utilized by the CDC for their investigation and Epidemiology Report.

Patients were identified through the hospital’s emergency room log, by nursing personnel, and by staff physicians who admitted patients to the Hospital during the outbreak period and met the case definition. Affected hospital employees identified family members with similar illnesses, and notification about the outbreak to the community yielded additional cases. Anyone identified was interviewed in person or by telephone by one of the CDC investigators. In addition, the patient’s physician was interviewed and medical record reviewed. Demographics, employment data, personal habits, illness signs and symptoms, past medical history for lower extremity vascular disease, family history of phlebitis and the epidemic illness were obtained. Sixty-one patients were primarily reviewed for this report.

Method for follow-up employed a questionnaire designed to assess the health status and ability to work. Of the original 61 patients, 17 were lost to follow-up, fourteen were deceased, and 30 available for survey. The Principal Investigator had attended seven of the deceased until their death, and all 30 patients were seen routinely until his retirement in 2005. Twenty of the patients completed the questionnaire at time of physical exam. The remainder were interviewed by phone and sent questionnaires that were returned via US or electronic mail.

Patients were given a list of symptoms that characterized the 1975 outbreak and asked whether they experienced the symptoms: never, frequently, or always. Using a scale from 1 (most) to 7 (least), patients completed a Wellness Assessment
identifying those symptom(s) that were the largest barrier to wellness. Patients then chose whether they felt well again within one year of illness, within five years, within 10 years, within 25 years, or never. Lastly, patients subjectively rated the degree to which their health returned by choosing decrements 100%, 75%, 50%, 25%, or never and whether they were able to return to work. Laboratory tests were not performed for the follow-up study.
RESULTS

CDC Findings of Initial Outbreak

The CDC identified 45 epidemic cases between August 1 and September 30, 1975. Forty of these were hospital employees, four were non-hospital contacts of ill employees, and one was a woman hospitalized in the Intensive Care Unit for 6 days between August 19 and 24. Of the forty employees, 10 were full-time ICU nurses, 2 were part-time ICU nurses, and the remaining 28 worked in other areas of the hospital. Figure 1 represents the Epidemiology Curve for the number of cases and date of onset, and Table 2 illustrates the attack rate for the 40 cases as determined by the Public Health Service of the Center for Disease Control (Epidemiology Report 76-21-2, 01 Dec 1975). No etiologic agent could be identified. An addendum to the below summary report noted that an additional 15 cases were reported by November 20, 1975. None were ICU employees.

CDC Epidemiology Report Summary

“Between August 1 and September 30, 1975, 40 cases of an unusual illness were noted among the employees of a Sacramento hospital. Four additional cases occurred in family contacts of ill employees and one in a hospital patient. The illness was characterized by leg pain with tenderness along the saphenous veins, often associated with nausea, headache, diarrhea, and mild fever. Physical examination showed palpable cords in some cases, but there were no consistent findings. Five of eight biopsies of perivenous adventitial tissue showed perivascular cuffing with mononuclear inflammatory cells, but all other laboratory studies failed to show significant abnormalities.

The highest attack rates occurred among Intensive Care Unit nurses and ward clerks.”
Epidemiologic investigation showed a significantly higher rate of smoking and use of oral contraceptives among cases than controls. Extensive study failed to identify an etiology or mode of spread. The etiologic hypotheses considered were: 1) infectious disease, 2) undetected toxin, and 3) psychosomatic illness.

The outbreak resembled closely the episodes of epidemic phlebodynia described in West Virginia and Montana in 1953 and 1961.”

After the initial CDC and California State Department of Health investigations, an additional 176 hospital employees were identified. Among 696 hospital employees, 216 epidemic cases were identified. Ages ranged from newborn to 59. Among these, twenty-three children became ill. Pediatric cases were routinely mistaken for mundane upper respiratory infections. This led to later examination and fewer overt vascular features. Nineteen children, from secondary to quintary cases, required home tutoring. There were two probable in-utero transmissions in secondary cases. The ICU and the Supply departments had the greatest number of epidemic cases.

Description of the 1975 Outbreak

Demographics for the 61 epidemic cases chosen for this report are summarized in Table 3. Table 4 delineates acquisition dates and disease transmission. The illness spread from 29 epidemic cases to 84 other individuals including family members, patients, and one physician and his private practice office staff. The entire families of patients E8 and E60 became ill, including E8’s son-in-law.

Figure 2 illustrates the monthly onset during 1975 for 58 patients. The onset could not be determined in three cases. Most cases clustered July to November, peaking in September. The infection rate for all who became ill was 8.8% in 136 males and
16.8% in 560 females. In 22 epidemic cases the mean incubation period was 17.4 days and the median 15 days.

Initiated by an unknown agent, the epidemic was heralded by a severe, prolonged, flu-like stage. Hallmarks were fever; flu-like symptoms; severe, generalized pain; and painful inflammation and swelling of the lower, and later, upper extremity veins. Signs and symptoms included arthropathy, decrease in cognition, gastrointestinal dysfunction, lymphadenopathy, myopathy, neuropathy, encephalopathy, vasculopathy, environmental sensitivity, sicca symptoms (Sjogren syndrome, an autoimmune disease causing dry eyes, dry mouth, and associated with a connective tissue disorder such as rheumatoid arthritis), conjunctivitis, dyspnea (shortness of breath), intolerance of normal activity, energy absence, recurrent sinusitis, recurrent pharyngitis, and hair loss. Secondary to quintary cases had less overt venous involvement. In these cases superficial vascular features largely regressed before diagnosis. Tertiary to quaternary cases, presenting with mild symptoms, were examined later when the superficial venous involvement had largely resolved.

Venous findings included painfully swollen veins, vein rupture, petechial eruptions, bluish discoloration of extremities, purpuric lesions showing venulitis, venous spasm, venous thromboses, venulitic skin eruptions, abnormal I-123 fibrinogen scans, impaired pulmonary diffusion (without pulmonary disease), edema, and reduced temporal blood flow by neuroSPECT scanning (4,5). Forty-five nurses were admitted to Mercy San Juan Hospital with presumed thrombophlebitis. Dye contrast venograms in four and Doppler studies in three revealed patent veins. Six young women had strikingly abnormal, swollen veins over the upper inner arms and thighs. A blue band was found on the volar (palm side) surface of the forearms in 76%. In
**E20** and **E53**, lower extremities and feet swelled suddenly and regressed within hours to several days. Thenar eminence veins (Figure 3) were deeply blue and engorged in 98% of the patients. Vein rupture occurred in all extremities. It was difficult to infuse one outpatient and two ICU patients, implying venous spasm. Surgery on one revealed the vein to be patent, but in spasm. Venous discomfort was frequently described as “a hot poker being pushed through the veins”. The Rumpel-Leede sign (distal shower of petechiae that occurs immediately after the release of pressure from a tourniquet or sphygmanometer) was present in 83% of study cases. Palpable purpuric lesions, at their worst, showed central necrosis (Figure 4). Three study cases had painful, venulitic eruptions (Figure 5). Severe vasculitic lesions developed in **E8**, lasting eight years. In **E60** severe pelvic pain led to laparotomy with normal findings, but subsequent I-123 fibrinogen scanning showed grossly inflamed iliac veins (6,7).

Lymphedema was common, sometimes massive, precipitous, and unresponsive to diuretics. It often resolved in hours to days. Autoimmunity, usually mild, was severe in three cases.

Hearing was intermittently impaired, partly from severe tinnitus. **E8** became permanently deaf. Ninety-three percent of patients had striking ptosis (drooping eyelid caused by muscle weakness) of eyelids during relapse with eyes reduced to mere slits (Figure 6A). When in remission, the patients would often appear normal (Figure 6B). **E4** frequently had to hold her eyelids open in order to read.

Muscle fasciculations (involuntary muscle contraction and relaxation visible under the skin), gross tremors and overt shakes were often dramatic. Spasm at times was
striking. Severe weakness caused falls. Grasp was weak; containers could not be opened and items were often dropped. At the worst the head could not be held upright. E13 had prolonged right foot drop.

Initial flu symptoms ranged from one to more than 104 weeks. Disease expression varied. Fever, often prolonged and continuous, reached 105°F. Relapses were often worse than original onsets.

Treatment was unsuccessful and ameliorative at best and included transfer factor, levamisole, and steroids (8-11). Severe headaches, unresponsive to even the most potent opioids, accompanied by nausea and vomiting, led to dehydration and lengthy hospitalization. Musculoskeletal chest pain caused patients to frequent emergency rooms, fearing angina. Suicidal ideation was common, and one surgical nurse committed suicide in 1987 due to uncontrollable pain.

Patients had profuse sweating, bright red palms, frequent urination, and cold or violaceous hands. Peptic ulcer symptoms were common, and six had overt ulceration. Joints were mildly swollen, grossly in E10. Foot pain was described as “walking on bare bones”.

Tests and biopsies were conducted as available and as methodologies evolved (Table 5). Most studies were performed post-initial flu illness and some after 1990. Biopsy of veins showed thickened walls in five and perivascular cuffing with immune cells in twelve. Eight exhibited inflammation of venules on biopsy of purpuric lesions, four of which showed leucocytoclastic venulitis (Figure 7). Eleven spontaneous thromboses occurred in eight patients, two in deep circulation. E10 suffered three
superficial thromboses, one on the dorsum of the right hand. \textbf{E8} also had a thrombosis on the dorsum of the right hand.

I-123 fibrinogen scans were performed at University of California Davis from 1976-81. These showed inflammation of the veins that improved with time. Only one was positive after 1978. Figure 8 illustrates two scans of \textbf{E8}, one done in 1976 and the other in 1978. Concurrent contrast venograms and venous dopplers indicated patent veins. NeuroSPECT scans were abnormal primarily in temporal areas. Arthropathy was periarticular (tissues surrounding a joint). Eosinophilia, as high as 33, occurred only during the early outset of the outbreak. Electromyograms showed both sensory and motor impairment. There were many fluctuating abnormalities in keeping with active viral infection.

\textbf{Representative Patient}

\textbf{E53}, a 32 year old Caucasian female, ECG department head, experienced flu-like symptoms for 12-months. The patient fell repeatedly from dizziness, weakness, and lack of muscle control. Her falls resulted in severe injuries. Her pharynx was erythematous. She was febrile to 102˚F at the onset and intermittently thereafter. Cognition was severely impaired including expressive aphasia and gross confusion. She experienced 30 documented episodes of mid-conversation spontaneous sleep, head falling on her chest, and in a coma-like state. Precipitous swelling of a single lower extremity occurred, often for hours to several days. Fluttering sounds and roaring in the ear diminished her hearing. She stated she sometimes felt she was “being struck in the head with a hammer”. Emotionally fragile, she became a recluse.

Striking venous features included engorged, indurated, painful, pencil-like, deep blue
veins next to the thenar eminence (see Figure 3); blue thenar eminences; and a
distinct blue band on volar forearms of 6 cm width, extending two-thirds of the way to
the elbow. In 1979, 20-minute cycles began of rapid, painful, hot engorgement and
then emptying of arm veins occurred. Under direct observation in June 1982, she
developed two spontaneous, palpable, purpuric lesions of the left arm. Generalized
petechial eruptions were recurrent; Rumpel-Leede sign was markedly positive; and
she had occasional sudden, violaceous discoloration of the anteromedial knees.
Biopsies revealed: purpuric lesion—leukocytoclastic, lymphocytic perivascular
dermatitis; lymph gland—hyperplasia; and wrist nodules—fasciitis, muscle-fiber
necrosis and type II atrophy. She suffered three superficial and one deep
thrombosis of an extremity, causing a pulmonary embolus. In February 1986, a
cerebral MRI showed demyelination. A second MRI in June 1987 revealed
additional areas of demyelination, including the right parietal lobe.

30-Year Follow-up

Continued ill health was notable in the follow-up patients. General symptoms of
fatigue, weakness, and muscle pain; vasculopathy; cognitive and neurological
dysfunction; joint discomfort, painful swelling of lymph nodes, and ulcer symptoms
remained significant. Table 6 highlights those symptoms still present in at least half
of all patients. Environmental sensitivity to heat and cold, humidity, odors, and
petrochemicals continued. Recurrent sinusitis and hearing impaired by tinnitus
declined minimally. Impaired vision due to ocular muscle dysfunction and
photophobia declined by one-third. Eighty-one percent of patients complained that
activity intensified many of their symptoms; forty-three percent had recurrent fevers;
and 32 percent suffered from inflammation of the eye.
Although other symptoms of the 1975 outbreak were present to some degree in follow-up patients, overall relapses had become milder after 30 years. Venous findings had receded but were still present. Leg pain due to inflamed deep veins and palpable purpuric lesions, often painful even before eruption, affected a majority of the patients. Many of the severe neurological findings also decreased except transient ischemic attacks (44%) and those noted in Table 6.

The largest barriers to wellness (Table 7) included general pain, lack of energy, and confusion and memory loss followed by neurological sequelae, headache, and painful veins.

Twenty-two patients cited pain as their chief complaint; four cited cognitive dysfunction.

Only one patient reported feeling normal again within one year of illness and rated the degree to which health returned as 100%. Interestingly, despite presenting with severe dementia at the time of the outbreak, this patient did not have the adverse venous involvement. The remaining 29 never felt they fully recovered. When asked to rate the degree to which their health did return: one responded 75%, seven responded 50%, one responded 25%, and 20 felt it never fully returned. The overwhelming majority of patients who reported energy absence required significant bed rest, and fatigue precluded work activity. Figure 9 depicts the degree of disability for all epidemic patients. Many of the patients reported permanent disability to the attending physician prior to 2005-2006. Follow-up patients reported that energy absence coupled with decreased cognition, extreme drowsiness, falling episodes, dropping items, and impaired vision and hearing had precluded work.
Seventy-five percent of the patients were permanently disabled and did not work again after the onset of their illness. Eight of the living had been or were currently able to work; however, five of those worked only with great difficulty.
DISCUSSION

This report documents the thirty-year history of a 1975 community hospital outbreak that affected ICU nurses and hospital staff and spread to other healthcare workers and outsiders. The large number of secondary to quintary cases inferred communicability and implied latency. The viral-like epidemic was marked by pronounced venous inflammation, pain, flu-like symptoms, severe exhaustion and weakness, impaired cognition, nervous system abnormalities, unpredictable relapses, and disability. No etiologic agent could be identified by the Centers for Disease Control and Prevention despite laboratory evidence of on-going infection. The higher rate of smoking and use of oral contraceptives noted by the CDC in their investigation may highlight a predisposition to the venous complications observed in this outbreak.

A literature search at the time of the 1975 Mercy San Juan Hospital outbreak revealed three previous reports of Epidemic Phlebodynia (painful veins) predominately affecting nurses and other hospital workers (1-3). In 1953 Pearson reported a group of 19 student nurses and 3 graduate nurses from St. Mary’s Hospital in Huntington, West Virginia who presented during the fall and winter of 1950-1951 with incapacitating pain and exquisite tenderness along the course of the superficial venous tracts of one or more extremities. Pearson found veins to be patent but with thickened walls, subacute phlebitis limited strictly to the vasa vasorum with invasion of inflammatory cells and perivascular cuffing (accumulation of lymphocytes or plasma cells in a dense mass around the vessel), and leucocytic thrombi containing eosinophiles and polymorphonuclear cells. Endothelial swelling and edema were noted in vessels without thrombi. These vascular findings were similar to those of the epidemic reported here. Additionally, the I-123 fibrinogen scans performed at University of California Davis corroborated these findings.
In contrast to the 1975 outbreak, the illness reported by Pearson was self-limiting with fewer flu-like symptoms and no evidence of lymphedema or lymphangitis. The outbreaks reported in 1961 and 1965, although presenting similar vascular findings to the 1953 outbreak, had more flu-like symptoms, were more widespread and familial, longer in duration, and had a relapsing course. Interestingly, the extent and features of the vascular involvement seemed to evolve with each subsequent epidemic outbreak. Epidemiologic, clinical, and laboratory investigations of those and this outbreak failed to establish an etiologic diagnosis.

The communicability, myriad of diverse symptoms and organ systems involved in the 1975 outbreak were similar to reported epidemic cases of Myalgic Encephalomyelitis (12-15), Epidemic Neuromyasthenia (16-18), and Chronic Fatigue Syndrome (19-22). In the 1934 outbreak of Myalgic Encephalomyelitis reported by Gilliam (23), the mode of spread was unknown and characterized by marked disability, intolerable pain, and the presence of psychotic ideation. No reports of ME, ENM, or CFS describe the significant venous features characteristic of this outbreak. Leon-Sotomayer only briefly referred to prominent veins and purpuric areas (24). Pellew and Miles indicated vascular pathophysiology but made no mention of venous inflammation (16,25). Spence cited leg discoloration suggesting vascular inflammation (26). While other diseases such as Fibromyalgia (27,28), multiple sclerosis (29), systemic lupus erythematosis (30,31), post-polio syndrome (32-34), Lyme disease (35), and cancer (36) have certain similar features to this outbreak, they differ in laboratory test results and in presentation. Other causes of painful and thrombosed veins (37,38) are not applicable to this setting.
Viral etiologies can be responsible for systemic vasculitis. It is well recognized that infectious agents and/or their components can directly and/or indirectly cause inflammatory vessel wall damage or vasculitis through a variety of pathogenic mechanisms (39). Vasculitis is an inflammatory process, and its symptoms are dependent on the severity of the inflammation and the organ system(s) affected. Some forms are so mild that the only symptoms noted are petechiae (small 1-2mm red or purple spot on the body caused by a minor hemorrhage). In more widespread types of vasculitis, general symptoms may include fever, achy muscles and joints, decreased appetite, weight loss, and loss of energy. Organ involvement may include skin, joints, central nervous system, gastrointestinal system, kidney, lungs, and heart. Although the tests available then and today do not firmly establish the diagnosis of vasculitis, positive laboratory studies such as the rise and fall of IgM; lymphocytosis; monocytes; neutrophilia; elevated alpha interferon, C-reactive protein, erythrocyte sedimentation rate; and upregulated 2-5A synthetase/RNase L pathway suggest the presence of an infectious agent. This is further substantiated by the cutaneous vascular symptoms, pain, illness severity, and involved organ systems reported in this epidemic. As outlined in Table 5, many of the above mentioned studies were performed, but failed to show anything definitive.

Although the hallmark symptom of profound venous vasculitis in this epidemic outbreak is not fully understood in context to the spectrum of illnesses defined as CFS, it is most likely related to a viral etiology. Viruses have been associated with infectious vasculitis and CFS, and interestingly many of their symptoms overlap. Upregulation of 2-5A Synthetase/RNase L antiviral pathway has been measured in extracts of peripheral mononuclear cells from CFS patients suggests an activated immune state and a role for persistent viral infection in the pathogenesis of CFS (40).
Additional research has linked CFS with a retrovirus (41), although three follow-up studies failed to support this finding (42-44). In the present report the vascular inflammation appears to be an early presentation and possibly related to the virulence of the disease since it is most severe in primary and secondary cases and mild in tertiary to quintary cases.

The vasculitis could also be related to cardiovascular abnormalities associated with CFS including reduced cerebral perfusion, orthostatic hypotension/tachycardia, and impaired lower limb venous innervation (45,46). A relationship between low-grade inflammation, oxidative stress, and arterial stiffness has also been demonstrated in CFS patients (47). Vasculitis reactions are more likely if the blood flow is reduced. Mediators of inflammation such as antibodies and complement circulate in the bloodstream and are more likely to adhere to the vessel wall resulting in vasculitis. In previous reports of ME, autonomic vasomotor instability and impaired blood flow in the microcirculation were noted (48,49). References to vasculopathy also appear in the major textbook on ME edited by Byron Hyde (50). A gene expression study identified seven subtypes of CFS in which genomic analysis revealed some common (neurological, hematological, cancer) and some distinct (metabolic, endocrine, cardiovascular, immunological, inflammatory) disease associations among the subtypes (51). The vasculitis may be associated with a specific subtype. This may also explain the wide spectrum of symptoms noted in CFS patients as well as the symptomatology specific to this outbreak.

Descriptions of published outbreaks of Epidemic Phlebodynia, Epidemic Neuromyasthenia, Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, and similar illnesses known by other names occurring in the United States and worldwide
suggest the possibility that CFS may be the illness described in 1975. It was not until 1988, more than 10 years after the Mercy San Juan Hospital outbreak that researchers at the CDC proposed the name Chronic Fatigue Syndrome after investigating the 1984 outbreak of ME in Lake Tahoe (52). The clinical definition was revised in 1994 (22). Once laboratory evaluation and physical examination rule out other illnesses, the diagnosis of Chronic Fatigue Syndrome may be made if (1) clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e., not lifelong), is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities and (2) the concurrent occurrence of four or more of the following symptoms: substantial impairment in short-term memory or concentration; sore throat; tender lymph nodes; muscle pain; multi-joint pain without swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and post-exertional malaise lasting more than 24 hours. These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue. The Canadian clinical working definition established in 2003 identifies fatigue; postexertional malaise; sleep dysfunctions; pain; and neurological/cognitive, autonomic, neuroendocrine, and immune manifestations (53). The Royal Australasian College of Physicians established Clinical Practice Guidelines on the evaluation of prolonged fatigue and the diagnosis and management of CFS in 2002 (54). In 2007 the United Kingdom National Institute for Health and Clinical Excellence also published a multidisciplinary clinical practice guideline (55). Since 1999 the Japanese have held various symposia and workshops on CFS and fatigue science (56). Despite all the worldwide attention, its myriad of symptoms, unknown etiology and diagnosis by exclusion makes ME/CFS identification challenging.
The patients in this report demonstrated generalized pain; energy absence and severe fatigue; confusion, memory loss, other neurologic problems; and leg discomfort resulting in significant disability, and inability to work. According to the CDC, disability in CFS patients is comparable to those with multiple sclerosis, AIDS, lupus, rheumatoid arthritis, heart disease, end-stage renal disease, and chronic obstructive pulmonary disease (57,58). Functional capacity varies, and only 5-10% fully recover (59-61). Moreover, a systematic review found that in the synthesis of reported studies, 42% of patients were employed, 54% were unemployed, 64% reported CFS-related work limitations, 55% were on disability benefits or temporary sick leave, and 19% worked full time (62).

Thirty-year data, observational reporting, and possible patient and hospital bias warrant discussion. The present report deals with an epidemic outbreak that was identified, investigated, and findings formally documented and published in the CDC Epidemiology Report in 1975. At the time of the outbreak Chronic Fatigue Syndrome was stigmatized as a psychiatric illness and not recognized or defined by the CDC. Today the CDC recognizes CFS as a serious illness and launched a campaign in 2006 to raise public and medical awareness (63,64). This recognition lends serious credence to this report that would not have been possible 30 years prior.

CDC epidemiology officers utilized retrospective case controls generated by the California Health Department to assess the outbreak. While appropriate to investigating an outbreak, epidemiologists most often use observational designs. Descriptive studies permit estimation of disease frequency, time trends, identification of diseased individuals, and generation of an etiologic hypothesis (65). The
epidemiology literature is replete with observational studies, and the CDC funded a workshop to develop and recommend guidelines for reporting meta-analysis of observational studies in epidemiology (66). Dissemination of the present report in the peer-reviewed literature will be critical for any future meta-analysis of outbreak epidemics that resemble Epidemic Phlebodynia, Epidemic Neuromyasthenia, Chronic Fatigue Syndrome, and/or Myalgic Encephalomyelitis.

Finally, litigation ensued between patients and the hospital (Principle Investigator, personal communication). Patients were considerably demoralized by attempts of hospital staff, doctors, and attorneys to discredit their illness in order to defeat their claims for disability. This caused the possibility of bias in patients reporting the extent of their pain, discomfort, and other symptoms. However, since the Investigator had followed the study patients for 30 years; symptoms did not significantly abate or resolve; and CFS was reported in numerous outbreak epidemics worldwide, the possibility of patient bias is considerably less distinct.

In summary, while the outbreak had many features resembling the documented diseases described in this report, the “infectious venulitis”, severity of pain and symptoms, and long-term disability suggest that it may be a more virulent form of these illnesses or that the outbreak may represent a new disease entity. Indeed, the observed vasculopathy, severe generalized pain, dementia, severe neurologic findings, and peri-articular disease may suggest that this illness is disparate from CFS. Regardless, the information gleaned from the 1975 outbreak will add to the growing body of literature to an illness that has long been trivialized despite its devastating sequelae.
FIGURE LEGENDS

Figure 1. Epidemiology curve represents the number of cases by date of onset between August and September 1975 (Public Health Service, CDC, Atlanta. EPI 76-21-2. 01 Dec 1975). Hatched bar indicates hospital admission; star inserted into bar represents an Intensive Care Unit Nurse.
**Figure 2.** The monthly onset of illness during 1975 is depicted for 58 of the epidemic patients.

![Month of Onset](image)

**Figure 2**

**Figure 3.** Thenar eminence veins are illustrated. Part of the hand and wrist is blue from venous distention. (Verbal and written consent to use photograph were obtained from the patient by Dr Ryll, attending and treating physician.)

![Hand with venous distention](image)

**Figure 3**
**Figure 4.** Palpable and usually painful purpuric lesions showing central necrosis is illustrated. (Verbal and written consent to use photograph were obtained from the patient by Dr Ryll, attending and treating physician.)
Figure 5. Venulitic eruptions are illustrated. (Verbal and written consent to use photograph were obtained from the patient by Dr Ryll, attending and treating physician.)
Figure 6A and 6B. A striking example of ptosis of eyelids with eyes reduced to mere slits during relapse as compared to a normal appearance during remission. (Verbal and written consent to use photograph were obtained from the patient by Dr Ryll, attending and treating physician.)

Figure 6
Figure 7. Biopsy of purpuric lesions exhibited inflammation of venules with leucocytoclastic venulitis.
Figure 8. Comparison of I-123 fibrinogen scans from 1976 and 1978 demonstrating inflammation of patent veins.
Figure 9. Graph depicts the extent of disability experienced by the entire cohort of epidemic patients. The attending physician noted disability in many of the patients at the time of last contact prior to 2005-2006.
Table 1. Case Definition

**Epidemic form**
1. Major criteria
   a. Engorged, painful veins
   b. Flu-like prodrome
   c. Severe pain, usually generalized
   d. Pain on palpation of veins
   e. Purpura, palpable
2. Minor criteria (5 out of 10)
   a. Vein rupture
   b. Bluish extremity discoloration
   c. Thromboses
   d. Petechial eruptions
   e. Venous spasm
   f. Rumpel-Leede sign
   g. Impaired pulmonary diffusion (in absence of lung disease)
   h. Lymphedema
   i. Dementia
   j. Neurologic features

**Secondary / Sporadic form** – as above with two exceptions
1. With / without viral onset
2. With / without superficial vascular phenomena

Case definition for initial outbreak and secondary and sporadic forms. Venous involvement encompassed distended painful veins, painful and raised purpuric lesions, rapid filling and emptying of veins, spasm of veins and inability to infuse, blueness of arms and elsewhere due to venous distention, presence of thenar eminence veins, unusual appearance of engorged veins in arms, legs, and thighs.
Table 2. Attack Rates for Epidemic Illness Based on ICU Exposure*

<table>
<thead>
<tr>
<th>Category</th>
<th>Ill**</th>
<th>Total</th>
<th>Attack rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU nurse, full-time</td>
<td>10</td>
<td>20</td>
<td>50.0</td>
</tr>
<tr>
<td>ICU nurse, part-time</td>
<td>2</td>
<td>10</td>
<td>20.0</td>
</tr>
<tr>
<td>Non-ICU employees</td>
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Attack rates for epidemic illness based on ICU exposure (*Public Health Service, CDC, Atlanta. EPI 76-21-2. 01 Dec 1975).

**Applying case definition (Table 1) and using case finding methods (pg 6) outlined by the CDC, these patients were identified during the outbreak investigation.

Table 3. Patient Demographics

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<thead>
<tr>
<th></th>
<th>Epidemic Cases</th>
<th>Follow-up Cases</th>
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Patient demographics at the time of initial epidemic outbreak and at 30-year follow-up.
Table 4. Acquisition Dates and Disease Transmission

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Acquisition dates and disease transmission for primary through quintary cases. The patients are listed according to source of exposure and date of illness. An alternating number and letter system is used to show the spread of the disease.

*F, Female; M, Male
†HCP (health care provider; i.e. physician, nurse, nursing aid, nursing asst. dental asst); FSP (facility service provider; i.e. ward clerks, clerical staff, housekeeping staff, other non-patient care staff); AHCP (ancilliary health care provider; i.e. ECG and laboratory technicians, phlebotomist); POS (physician office staff); NPOOC (non-patient physician office contact)
Table 5. Laboratory and Environmental Studies

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<td>Muscle</td>
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<th>TC 99 M-phosphate, bone</th>
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Tests and biopsies conducted as available and as methodologies evolved in the 61 epidemic patients.
Table 6. 30-Year Follow-up*: Symptoms Marking the 1975 Outbreak.

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<td>COGNITIVE DYSFUNCTION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired concentration</td>
<td>4</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Impaired short-term memory</td>
<td>6</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Uncontrollable Drowsiness</td>
<td>9</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>NEUROLOGIC DYSFUNCTION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>11</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Dropping Items</td>
<td>7</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>ARTHROPATHY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint Discomfort</td>
<td>4</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>LYMPHADENOPATHY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful swelling lymph nodes</td>
<td>11</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>GASTROINTESTINAL DYSFUNCTION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcer Symptoms</td>
<td>8</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

Symptoms experienced by at least 50% of the follow-up patients are listed in descending order of frequency within each symptom category.

*Patients did not respond to all questions

**Percent calculation = Yes (Frequently+Always) Responses divided by Number of Respondents
Table 7. 30-Year Follow-up: Wellness Assessment*

<table>
<thead>
<tr>
<th>Which Symptoms Most Keep You From Feeling Well?</th>
<th>Median</th>
<th>25 Percentile</th>
<th>75 Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Pain</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lack of energy</td>
<td>3</td>
<td>1.5</td>
<td>4</td>
</tr>
<tr>
<td>Confusion, memory loss</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Neurologic</td>
<td>4</td>
<td>1.5</td>
<td>5.75</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Painful veins</td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

*Scale 1-7; 1 = largest barrier to wellness, 7 = the least
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