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Notes	In 1956, Henderson was part of an EIS investigation of one of the first recognized outbreaks of what was then called "Iceland Disease". See Henderson DA, Shelokov A (1959). *Epidemic neuromyasthenia; clinical syndrome, parts 1 and 2* . NEJM 260(15): 759-64 & 260(16) 814-8 The investigation was also the subject of Berton Roueché's *In the bugouse* , published in he New Yorker (27 Nov 1965, 205-cont) .
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REFLECTIONS ON EPIDEMIC NEUROMYASTHENIA (CHRONIC FATIGUE SYNDROME)

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Keynote Address for the First International Chronic Fatigue Syndrome Conference

Albany, NY

October 3, 1992

Keynote Address

Reflections on Epidemic Neuromyasthenia (Chronic Fatigue Syndrome)

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Jay Levy's invitation to speak at this International Conference on the chronic Fatigue Syndrome came as an all but forgotten echo of the past. It was a welcome one, however. Epidemic neuromyasthenia -- the candidate name which Alexis Shelekov and I proposed for the syndromes we had studied -- was a recurrent preoccupation for us both over a number of years, as I shall relate. There weren't many who shared that interest. In fact, a meeting of North American scientists interested in the problems in the late 1950's could be and usually was held in my hotel room. However, my interest had to be put on hold somewhat over a quarter century ago

when various powers that be decreed I should devote my time to coping with smallpox.

After 11 years as an eradicator, I returned to the United States and the preoccupations of a Dean at Johns Hopkins University. Then, in the mid-1980's, newspaper accounts appeared of a mysterious epidemic on the California-Nevada border. The epidemic sounded suspiciously like those which we had investigated and reviewed 25 years before. The Centers for Disease Control (CDC) investigators alluded to certain other outbreaks with similar characteristics but made no reference to the epidemics of the 1950's. I suggested to former CDC colleagues that the investigators might benefit from reading our New England Journal of Medicine review article. In due course, I received a telephone call from CDC asking where the review article had appeared. I cited to them the 1959 article and heard in response: "We did not know it was <u>that</u> long ago. In the literature search, we only went back to 1965." Although I do appreciate the fact that I am not so young as I used to be, I do not appreciate my earliest papers being treated as some form of pre-history.

Whatever, you have asked for reflections on certain pre-historical, pre-biotechnology outbreaks and I shall do my best aided, in part, by certain dusty files which were reread after several decades of quiet moldering. I should note, in passing, that you have done irreparable damage to my wife's campaign to chuck at least a few of those ancient files which "have not been looked at in years."

Beyond the events directly connected with the studies themselves, there were several interesting circumstances which bear relating as side bars to our frustrated efforts to understand and decipher a puzzling problem. Even Albany, New York, factors into this story.

My involvement with this syndrome began on May 9, 1956. I was then two years out of internship and completing my first year as Chief of the Epidemic Intelligence Service (EIS) at CDC. Alexis Langmuir's EIS was then five years old, mostly comprised of physicians discharging their compulsory military service. Few of us had more than a year or two of post-graduate training. On May 9, CDC received a letter from Dr. James Bond, the Florida State epidemiologist, which read as follows:

"We have recently received reports from local physicians in Punta Gorda of the occurrence of a disease syndrome quite similar to that in Tallahassee in 1954. Punta Gorda is a small town of approximately 2000 population on the lower Gulf Coast."

"Over the past ten weeks they have seen a total of sixty-four cases, all in white females of age 30 to 60 with the single exception of a white male age 70. The common symptoms are sharp, recurrent pains in the musculature of the cervical and thoracic spine and the shoulder girdle; severe headache, disturbances of coordination, and some transient motor and sensory nerve dysfunctions, apparently central in origin. Positive physical findings have been nystagmus, positive Romberg, asymmetrical hyperactive deep tendon reflexes, and in one case, a transient foot drop. Routine laboratory studies have been within normal range. Special virological studies on nine patients are as yet incomplete. Detailed epidemiological information is currently being collected on twenty-nine of the cases."

"The emotional overlay in the patients noted at Tallahassee is

again very apparent and confusing. However, all physicians, including one Board Internist, are agreed that the common anxiety neuroses of adult females cannot explain in entirety this syndrome."

Dr. Bond refers to the preceding Tallahassee epidemic, more correctly the Leon County epidemic. A word or two about it is important because it is one of the largest on record. Its investigation, conducted by Drs. Jim Bond and Harold Wolfe, the latter, Professor of Neurology at Cornell Medical School, was a thorough and searching one. A detailed manuscript was eventually prepared and a copy was sent to me but, so far as I can determine, it was never published. There is only a comparatively brief account in the Lancet.

The epidemic of some 460 cases begun in August 1954, peaked in late September and ended in November. It commenced about the time of a city-wide fund raising effort by the March of Dimes accompanied by much publicity and many pictures of polio patients. Perhaps in part because of this, many of the cases in the outbreak were reported as polio cases and, indeed, some were. Wolfe, however, believed that the polio cases were

readily distinguishable and considered the overwhelming majority of cases not to be polio.

This is a large number of cases for a county population which was then only 60,000. Nearly 70 percent of the cases were among women between 15 and 55 years of age; only 4 cases were reported among non-whites; none were reported among students of Florida State University. Almost all occurred as single cases in families. Among women 25-34 years, about 4 percent were afflicted. Eighty percent gave a history of contact with a proceeding case, on average 10 days before but with a wide range of intervals extending up to a month. Virological and serological studies, as you might expect, were of no help.

Bond and Wolfe entertained a number of possible etiological hypotheses but eventually concluded that it must have been caused by a virus, spread from person to person, with symptoms "modified by the physiological or serological differences that exist between youth and middle age, male and female, negro and white and perhaps married and unmarried."

Bond had neither the time nor inclination to get involved in yet another epidemic and so he had written to CDC to request help for the Punta Gorda investigation. I telephoned Bond to discuss arrangements -- yes, Virginia, there were telephones in those days -- and it was agreed that an EIS Officer, Dr. David Poskanzer, would undertake the study. David was then assigned by CDC to the New York State Health Department in Albany, New York. Subsequently, as you may know, David trained as a neurologist and was on the Harvard faculty at the Massachusetts General Hospital. His interest in epidemic neuromyasthenia continued until his death four years ago.

David left Albany immediately for Punta Gorda. There, with his customary vigor and enthusiasm, David characterized the principal symptoms, drew up a form and mobilized volunteers to undertake a city-wide survey. The Rotary, Lions and Kiwanis Clubs participated, as well as the Junior Women's Club and black school teachers. The number of cases then appeared to be more than 100.

After a week he came to Atlanta to report his preliminary findings to

participants in the annual EIS Conference. In candor, his account was greeted with healthy skepticism. He recounted the occurrence of multiple and protean symptoms, disturbances in memory and mentation, muscle weakness and tenderness, menstrual disorders, depression and other symptoms. Physical findings were sparse, often questionable or made little neuroanatomic sense. The laboratory findings were negative. A very basic question was what indeed defined a case. A number at the Conference drew the conclusion that he was doing little more than documenting a panoply of neuropsychiatric syndromes which might be found in any community.

For me, the presentation seemed all but incoherent and I could not help but wonder whether the problem might not be more that of an enthusiastic but inexperienced investigator than of a real disease.

Whatever, I decided we should return to the scene for further work but with specialized neurological expertise. We sought to recruit Dr. Harold Wolfe, the Cornell Neurologist who had worked in Tallahassee but he had not the time. He referred me to Dr. Charles Kunkle, Professor of Neurology at Duke, who joined David and I along with Dr. Sy Kalter, head

of virology at CDC.

We selected 21 reported patients for detailed clinical and laboratory examinations, a group we were to examine both five months and a year later. We also examined 22 persons chosen at random from some 62 cases which had been identified during the household survey.

I soon began to appreciate David's dilemma in defining a case. The patients were certainly varied in character. However, when we had completed a history and examination, the team was basically of one mind whether or not it was a case associated with the epidemic. One episode involving a patient is quoted by Berton Roueche in his New Yorker Annals of Medicine article. I quote Roueche who in turn was quoting me.

"I remember one case in point. It was a preacher -- white, middle-aged, and married. He had been sick, and his symptoms were generally provocative. Except on the emotional side. He insisted that there was nothing wrong with his mind or his memory. As we rose to go, the interviewer asked him if she could have a glass of water. Of

course, he said, and left the room. But almost at once he was back. The interviewer had asked him for something -- what was it? She told him. Oh, yes. He started out of the room again, and then stopped and called upstairs to his wife. Where did they keep the ice cubes? She told him, and he went on out to the kitchen. But a moment later he called her again. This time he wanted to know just how many cubes should go in the glass. We added him to the case list."

The few physical findings were no less a dilemma. Contrary to Bond's initial letter, we were unable to detect any patients with nystagmus, a positive Romberg sign, or abnormal deep tendon refleses. Patchy hyperesthesias occurred in half of the patients but they did not correspond to an area innervated by a discrete nerve or even several nerves. We would carefully map such areas on a patient's back and would return to find them unchanged <u>but</u> the following day wholly different areas were involved. One woman complained of recurrent subcutaneous modules but when we sought to palpate some, neither she nor we could find them. A day after examining her, she called to report that she had developed two more and we quickly revisited her. Sure enough, there were two tender pea-sized swellings on the

dorsum of the wrist. She agreed to a biopsy which was promptly done. The only problem was that the surgeon missed the nodule. Many patients complained of weakness -- paresis -- but reflexes were normal and the weakness seemed less organic than an unwillingness on the part of the patient to move the arm or leg.

It was difficult to judge the mental and emotional status of the more severely afflicted as we had no baseline of knowledge as to what they were like before they had became ill. The recurrent question was whether the symptoms were simply an overlay in a person who usually exhibited an array of neurotic symptoms or whether the symptoms, and the emotional affect were, quite new and different. Repeat visits over the year provided dramatic evidence of change in most and readily clarified in our minds the baseline status of most of the patients.

Throughout the course of the investigation, we entertained and explored every conceivable hypothesis -- toxic, psychologic or infectious and, if infectious, whether it was most probably common source, insect born, or spread from person to person. We believed then, and I believe now, that

the infectious agent theory best fit what we observed although none of the many virological or serological examinations offered us a clue as to which agent it might have been.

The syndrome, however, was impressive and alarming. I recall well being deeply concerned as I had never before been concerned during the course of an epidemic investigation -- the concern that in returning directly home, I might possibly serve as a vector to infect my wife.

Endeavoring to describe and characterize what we had seen proved difficult. None of us were especially comfortable with our definitions and the paper we prepared best summarizes this:

> "The illness epidemic in Punta Gorda illustrates problems inherent in an attempt to define a nonfatal illness with a broad array of symptoms that blend into the host of psychoneurotic and minor medical complaints endemic in a community. Although diagnostic criteria were established for purposes of analysis, accurate case delineation was not possible because of the nonspecific symptoms,

limited physical findings and negative laboratory studies. Cases with few symptoms, those with less pronounced manifestations and those occurring in the more stoical members of the community may have been omitted, whereas some suggestible, hyper-reactive and psychoneurotic persons may erroneously have been included. It is difficult, too, to determine which symptoms represent genuine manifestations of the illness and which are adventitious associations. A clearer picture of the disease may emerge only with additional outbreaks or with associated recognition of a specific diagnostic laboratory test."

We thought it presumptive to speculate on the possible pathology given the diverse symptomatology and the paucity of signs. Privately, we speculated that it represented, at least in part, some sort of autonomic nervous system dysfunction but we saw no way to demonstrate this conclusively.

Shortly after we had concluded the field investigations, I was contacted by Dr. Alexis Shelokov, then at the NIH, who had investigated a

similar type of outbreak some three years before in Rockville, Maryland. Alexis had planned to publish an article in the New England Journal and, at the same time, to prepare a Medical Progress Review article. He invited me to submit our article for contemporaneous publication and to join him as junior author for the review article.

As innocent and sensible as this arrangement appeared to be, repercussions followed at NIH, as he was later to tell me. The director of NIH specifically forbad him to publish jointly with a CDC scientist. CDC, in those days, was an inconvenient upstart, hardly a decade old and NIH senior staff wanted no part in according it status. The review, so Alexis tells me, represents the first joint NIH-CDC publication.

The 1959 Medical Progress review was intended to be published two years earlier, contemporaneously with our two epidemic outbreaks but Alexis developed hepatitis which incapacitated him for an extended period. He had completed a thorough survey of the literature but had no time to compile and analyze the material. Thus, it was agreed that I would do this. In recognition of this effort he insisted that I be senior author.

Alexis' literature review was a thorough one. One of the publications however, was of special interest. That was the 1934 epidemic, "diagnosed as poliomyelitis," at the Los Angeles County General Hospital. It was published as Public Health Bulletin Number 240 by the Government Printing Office and, as such, did not appear in the Index Medicus. It probably would never have come to notice accept for the fact that its author was Sandy Gilliam, then still alive and actively interested in science. Sandy brought this paper to our attention.

In preparing the review, I corresponded with a number of the investigators, including Sigurdsson, the author of the Iceland study, and Don Acheson who had been involved with the outbreak at the Royal Free Hospital. And, indeed, I sent to Acheson a draft of our review at his request. Much to my surprise, one week after our review appeared in the New England Journal, I found in the American Journal of Medicine a separate review prepared by Don Acheson. It was clearly his own analysis but the fact that the referenced outbreaks, including the Los Angeles epidemic, were the same is not coincidental.

There is one other side bar to recount which will wrap up the principal events surrounding Punta Gorda. In the spring of 1957, the American Epidemiological Society, the premier professional epidemiological society, decided that the Punta Gorda epidemic should be featured at its spring meeting -- where else but in Albany, New York. The AES, then comprised of 100 epidemiologists, provided for unlimited discussion of all papers presented. My 20-minute presentation was followed by more than two hours of the most searching and skeptical scrutiny. Indeed, I have never since had to present a paper under comparable stress.

In 1960, I returned to Atlanta and CDC after three years of residency and public health training to once again assume responsibility for the EIS. The question had remained with me as to what further steps we might take to elucidate the etiology of epidemic neuromyasthenia. We had had many different discussions with many different people. It seemed to us that we were dealing with either a new or an emerging problem of real concern. After all, the outbreak in Punta Gorda had immediately followed two other Florida outbreaks in Tallahassee and Bradenton. There was Shelekov's recent outbreak in Rockville as well as several in the United Kingdom.

Moreover, a further outbreak had occurred in Ridgefield, Connecticut which Alexis and I had investigated, albeit long after most cases had experienced onset of illness. Meanwhile, and subsequent to our New England Journal article, both of us had received numerous letters from individuals who believed themselves to have been victims. It seemed highly probable that there must be many other outbreaks which were not coming to attention and quite likely, a substantial number of cases occurring singly or in small clusters. We believed that between the New England Journal article, various press accounts, our many presentations to professional medical groups and contacts with state and local officials, we would readily uncover many more outbreaks. It seemed to us that one best line of attack on the problem was through study of cases at the time of first onset of symptoms or perhaps during the problem. In some respects, the syndrome resembled that which occurred among some after the acute phase of certain viral illnesses or suspect viral illnesses -- for example, hepatitis, infectious mononucleosis and influenza. As with influenza, at least, we suspected that by the time symptoms characteristic of the syndrome had developed and the patient had sought medical help, the etiological agent might well have vanished. Thus, the need to detect outbreaks and to investigate them early

on.

As we saw it, efforts to study individual cases of the syndrome to determine etiology had two drawbacks. One was the problem of differentiating between a presumably microbial-induced illness and an array of syndromes of psychogenic origins. None of us who had carefully examined patients in an epidemic setting felt confident in being able to accurately diagnose, cases which occurred sporadically. Moreover, from our 1959 review of outbreaks, it was quite clear that while the general characteristics of the syndrome in each of the outbreaks was similar it was equally clear that there were distinct differences from outbreak to outbreakin the prominence or even presence of many symptoms as well as their severity. A case definition embracing characteristics of all outbreaks would inevitably have to be so inclusive as to back any semblance of specificity. And that, parenthetically, was why we insisted on the modifier "epidemic". It was a note of caution, we were fearful -- I believe with reason -- that the syndrome would otherwise become a wondrous all emcompassing diagnosis for all manner of illnesses.

The second problem in dealing with individual cases was that we would inevitably be dealing with patients, days or likely weeks after onset, probably long after the etiologic agent or agents had vanished. The only logical approach seemed to us to be that of collecting and processing serial specimens obtained from patients-to-be in the prodromal period of illness and during the early acute phase. This necessarily would require investigation during the occurrence of an epidemic. Based on the epidemiology of the disease, likely candidates for such anticipatory sampling would be hospital staff or, in an institutional setting, still well persons who were in contact with cases.

We elaborated a protocol, discussed procedures to be followed, obtained agreements for participation by Kunkle and Wolff, alerted our field staff to notify us immediately of any suspect outbreak--and waited--and waited. The only outbreak to be detected over the next five years was that in a convent in upper New York State -- discovered far too late to permit specimens to be obtained.

So, where are we today? Since being invited to participate in this

conference, I have read a voluminous literature with great interest. It is all too apparent that although enormous advances have been made in biomedical research, the enigma of epidemic neuromyasthenia remains quite as puzzling a problem as it was 35 years ago.

Are we dealing perhaps with several agents rather than one? Possibly. As I revisit this frustratingly elusive syndrome, it now seems to me that there are two related but quite distinct questions. What is the pathophysiology of a "chronic disease syndrome" and what is its etiology or etiologies. The former question, that of pathophysiology can be addressed in case-control type studies because one can examine a range of functions and performance in individuals with the syndrome and those without. The latter question, that of etiology, poses quite a different set of quandaries. What is a case? A characteristic case in certain outbreaks would not meet case criteria in other outbreaks unless the definition were so vaguely stated as to encompass both cases and a far wider range of psychogenic disorders. Under such circumstances, searching for an etiological agent can be a futile exercise indeed. Personally, I see few options but to pursue that earlier strategy, conceived some 30 years ago, and that is to detect early and to

investigate cases as they occur in the course of an epidemic.

Meanwhile, is there a syndrome which you now call chronic fatigue syndrome? Was Punta Gorda real or imagined -- and what of all the others? As a clinician, I came away from my field experiences with the conviction that there is a very real illness, of infectious origin being transmitted from person-to-person and that some means for prevention or at least treatment of that illness was well worth pursuing.