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*Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome
Epidemic*

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woman and a fifty-seven-year-old man, were diagnosed within three days of each other in March 1983. The last victim received her diagnosis of non-Hodgkin's lymphoma in late July, exactly a year after her South African relative had been a guest in her home.

Grufferman established, too, that at least three and probably four of the lymphomas originated in the patients' B-cells, vital components, along with T-cells, of the immune system. The B-cell finding prompted the researcher to look for Epstein-Barr activity in the cancer victims' blood. As it turned out, only one of the three surviving patients had antibodies to the virus, indicating that the other two had escaped infection altogether. Whatever agent had caused the wave of cancer, then, it was not Epstein-Barr virus. Several other family members without symptoms of either cancer or fatigue were discovered to have elevated antibodies to the virus in a pattern that suggested reactivation of a latent infection, however. These apparently well family members had been exposed to some unknown pathogen that had harmed their immunity.

"It is possible that the Epstein-Barr virus was involved in some way," Grufferman concluded in his *New England Journal* article. "The symptoms of the visitor's illness suggested infectious mononucleosis, and her [blood] contained early antigen antibodies, thereby suggesting a recent or reactivated EBV infection. Secondly, several of the persons exposed had very high antibody titers to EBV." But because two of the three surviving patients had no evidence of exposure to the virus, Grufferman continued, "the data are most consistent with an unidentified transmissible agent, *with the findings of antibodies to EBV representing secondary activation responses*" (italics added).

In other words, a mystery virus, spread unwittingly by the South African to her hosts in America, had resulted in four cases of immune system cancer; the same bug simultaneously caused an immune system disturbance that allowed Epstein-Barr to be reactivated in other family members.

In a report to scientists at the National Institutes of Health many years later, Grufferman wrote that he and his collaborators initially dismissed the curious outbreak at Lake Tahoe as having nothing at all to do with the tragic events that had befallen the South African's American relatives. "We thought [the Tahoe epidemic] was part of the emerging picture of chronic fatigue syndrome," as the disease had then been named by federal scientists. But four months later the caller sent Grufferman a second clipping from the *Sacramento Bee* about a new outbreak of presumed Epstein-Barr virus associated disease in Placerville, California. Like Incline Village, Placerville was a community from which the caller lived a negligible distance and which she had visited.

"We then began to wonder whether she didn't have a point," Grufferman continued in his report, "and that her presence in the area might have been related in some way to the epidemics."

Incline Village, Nevada

Starting that fall, Peterson and Cheney began to observe an outbreak of rare immune system cancers not only among people who were ill with the epidemic disease but among other previously well residents of Lake Tahoe's north shore.

During the first week in November a fifty-four-year-old attorney who was Peterson's patient showed up in the clinic with a tumor at his jawline. The man had retired from an active law practice and now dwelt in the evocatively named Zephyr Cove, a community a few miles south along the lakeshore from Incline Village. Peterson sent the attorney to Stanford University's medical center for surgery. Following routine procedure, Stanford's pathology lab biopsied the tumor. Soon afterward, the surgeon who had performed the surgery called Peterson to inform him of the biopsy results. The mass was indeed malignant and the diagnosis most unusual: according to the pathologist who studied the cells, the attorney was suffering from Burkitt's lymphoma.

By the time an astonished Peterson called Stanford's pathology lab to discuss the finding, however, a second, more senior pathologist had studied the lawyer's tumor cells and changed the diagnosis to "undifferentiated B-cell lymphoma." The tumor cell's "architecture," the senior pathologist explained to Cheney some time later, did not display the regular, "brick-like" construction of a Burkitt's tumor. The tumor, in fact, failed to fit into any single category of B-cell cancer.

Buried in the parotid, or salivary, gland, a standard site for Burkitt's, the tumor had completely destroyed the tissues around it. "It was so distorted," the doctor remembered. "We asked to have it probed for Epstein-Barr virus, but they didn't have much to look at because it was such a destructive necrotic mass."

The lawyer's diagnosis prompted a flurry of speculation between Peterson and Cheney over whether his cancer might be related to the epidemic. The lawyer had not complained of severe fatigue, Peterson remembered, though there were hints of a problem during the year before his tumor appeared. "He had nothing that was marked," Cheney said. "On closer questioning," however, the doctor learned that "he had not been completely normal in the year leading up to this development. But he would not have said, 'I am very tired.' He would say, 'I don't have all the energy I used to.' It was that kind of thing. Nothing marked."

Acting on a hunch, Cheney ordered a magnetic resonance imaging brain scan on the attorney; the resulting image was one of the most pockmarked the doctor had yet seen. In the following months the attorney developed the chronic syndrome.

A week later a second previously healthy patient walked into the Alder Street clinic with a tumor on his neck. This thirty-eight-year-old plumber and handyman in a local casino had been a patient of Cheney's for two years. The plumber's tumor was also in the parotid, or salivary, gland, although it was a benign growth, characterized at Stanford as a "mixed salivary adenoma." (Adenomas are, by definition, benign, although they may become malignant.) Nevertheless, the Stanford lab probed the tumor tissue for Epstein-Barr virus at Cheney and Peterson's request and found it to be infused with the herpesvirus.

The plumber's diagnosis jogged Peterson's memory; one of his fatigue patients, a woman from San Francisco, had undergone surgery for the removal of a tumor in the parotid gland early in the course of her illness, which had begun two years before. That tumor too had been described as a mixed salivary adenoma. At the time, Peterson had thought little of the incident.

The implication of these uncommon immune system tumors arising spontaneously in the context of an epidemic characterized by immune dysfunction was

ominous. What if, as was sometimes the case in AIDS, lymphomas and other cancers were the inevitable culmination of this so far untreatable disease?*

The doctors were engaged in discussions about this possibility when the lawyer, who was recovering at home in Zephyr Cove, telephoned them with an alarming story. The attorney was calling to report the death from lymphoma of a six-year-old Los Angeles boy, the grandchild of a couple who lived in Zephyr Cove. The child had spent his Christmas season the previous year with his grandparents in Zephyr Cove. While in Nevada he had become debilitated by an illness for which none of the doctors his parents consulted in Los Angeles could find a name. The boy's lymphoma diagnosis came three months after his illness began. His older sister had spent Christmas in Zephyr Cove with her brother that year as well. She too became ill. Hers was a lengthy flu-like illness, much like her brother's; unlike her brother, however, the little girl had recovered.

Was it possible, the clinicians asked each other, that the siblings had picked up the bug that was just beginning its rampage through the north Tahoe area during the winter of 1984–1985 and had acquired the fatigue syndrome, except that in the boy's case, his immune system response was inadequate?

Then one of Cheney's favorite patients, a retired seventy-year-old engineer, complained to the doctor of a sudden onset of exhaustion that was keeping him housebound. On examination, Cheney found that the man had swollen lymph glands and low-grade fever. His Epstein-Barr virus antibodies were extremely elevated, and he was suffering from focal myocarditis, an inflammation of the heart muscle resulting in arrhythmias and heart murmurs. The principal causes of myocarditis are viral infections and rheumatic fever; Cheney was able to rule out the latter. Not surprisingly, the doctor suspected that yet another of his patients had contracted the Tahoe malady. The news was hardly welcome, but it was not astonishing. Six months later, however, the engineer's sixty-nine-year-old wife developed a malignant tumor mass on her jaw, which was diagnosed in Los Angeles as an "infiltrating, necrotizing B-cell lymphoma" of the parotid gland. Unlike her husband, the woman had no history of fatigue.

"I would say that to see—within one year—two B-cell lymphomas of the parotid gland was just unthinkable," Cheney said later. "I haven't seen that before or since. And I think the mixed salivary adenomas were unusual too."

The doctors were deeply alarmed.



Faced with the extraordinary possibility that the disease which had struck the north shore might be an epidemic of cancer, Cheney, in particular, began to mull the likelihood of spotting lymphomas at a presymptomatic stage. Was there a window of time, he wondered, when ominous changes at the cellular level could be detected, even interrupted? "I wondered if there was a test that could tell us what was going on in these people microscopically," the doctor said.

*In 1982 doctors in San Francisco had diagnosed nine gay men with Burkitt's lymphoma, a disease so rare that statisticians for the California Tumor Registry expect to find only two or three cases of the disease in the entire state every two years. The surge among gay men in San Francisco so impressed that city's infectious disease specialist, Selma Dritz, that she instructed the Centers for Disease Control to assume in the future that "Burkitt's lymphoma is a form of AIDS."

His queries led him to Susan Wormsley, a biochemist and flow cytometry expert at Cytometrics Laboratory in San Diego. Flow cytometry is an expensive, rarefied technology for quantifying and qualifying immune system cells; this technology is used to diagnose and stage the severity of lymphomas.

"Its value," Wormsley explained some time later in her sun-drenched office at Cytometrics, "is that it enables you to detect very small numbers of circulating abnormal cells whose presence, under a microscope, would be impossible to appreciate. What we do," she added, "you just couldn't do working under a microscope. You couldn't see enough. Flow cytometry is highly quantitative, very reproducible, and very sensitive," she continued. "The measurements are done on a single-cell basis—a *per cell* basis. That's really its strength."

Not long after establishing Cytometrics, Wormsley had begun to take advantage of one of the technology's most significant applications: monitoring the progression of B-cell lymphomas. In 1976 three Harvard scientists had developed the test, which was a highly sensitive method of finding monoclonal, or cancerous, B-cells in the blood. Called the kappa/lambda clonal excess assay, the test was able to detect lymphoma cells even when they were present in extremely low numbers.

"Say, for instance, a person normally had ten percent B-cells," Wormsley said. "If only one percent were abnormal, you wouldn't be able to find them using standard technology. But this test allows you to identify that one percent."

As helpful as it would seem to be, the kappa/lambda test was, for nearly a decade, a tool used almost exclusively by researchers rather than clinical oncologists. That was because, in late 1985, Cytometrics was the sole commercial lab in the country with the technical skill and equipment to perform it. Once Wormsley's expertise became known, there was a terrific surge of interest among oncologists in the region. Curiously, Wormsley found that the test's original function, which was to stage B-cell lymphomas, or determine how far the disease had advanced, was less frequently utilized by oncologists than was its secondary function, which was to identify microscopic changes that presaged the disease's onset. She devoted the lion's share of her time to evaluating very early B-cell lymphomas.

The biochemist thought she had seen every unusual result or combination of results one could see in a flow cytometer. Then, in December 1985, Paul Cheney called.

"Paul said he had this group of patients," Wormsley remembered. "And it seemed that, within that initial group, two or three went on to develop lymphoma. At that early stage, the worry was, 'My gosh, is this disease going to cause lymphoma in a *lot* of patients?'"

Wormsley asked Cheney to send her a handful of green tops, tubes capped with green rubber tops signifying that the anticoagulant heparin had been used to preserve the fresh blood. The clinician eagerly complied.

"We did a few samples," Wormsley continued, "and . . . there *were* abnormalities. But the abnormalities and the patterns we saw weren't really that similar to what you see in a patient who has lymphoma. These were very *strange* patterns. But they have been consistent over a long period of time for those given patients. The only problem is, we *still* don't know how to interpret what's going on."

One disparity between cancer patients and the Tahoe patients had to do with quantitative differences among the several categories of B-cells that circulate in the immune system. In the cancer patients, the differences were “very subtle,” Wormsley said. “In Paul’s patients,” she added, “we saw very large differences.”

“When I first saw some of these abnormalities,” Wormsley continued, “I said, ‘Wow! Send another tube of blood!’ And they did, and, *boy*, they were just *exactly* the same abnormalities! And now we’ve followed some of these patients out two and a half years, and they remain identical. They haven’t changed. It is a very worrisome finding.”

Cheney and Peterson began drawing blood from all of their epidemic patients and sending it to Wormsley.

“In the early stages we were getting three or four a week,” Wormsley recalled. “We also did some serially.” In most cases, the abnormalities remained stable in the same patients over periods of months and eventually years.

For Peterson and Cheney there was one problem: the kappa/lambda test cost \$400. On the frequent occasions when their patients’ insurance companies refused to reimburse them for the test or when an indigent patient was unable to pay, the doctors drew cash from the practice to cover the Cytometrics bill every month. Within two years Peterson’s personal debt to the lab was \$200,000.

After studying samples from approximately fifty patients, Wormsley estimated that the rate of clonal excess abnormality in the fatigue patients from Nevada was at least 25 percent. But that wasn’t the only aberration Wormsley found.

“Actually there were several abnormalities that we saw in these patients,” she continued. One was a voluminous amount of cell debris. “Right from the time we separated and stained the cells, we saw a lot of debris,” she said. “Just broken-apart cells, *pieces* of cells and platelets. And we don’t see that in anything else that gets sent to us. Now, naturally, with everything that is sent to us, the people are sick, and most of them have cancer—leukemia, lymphoma—but we didn’t see this kind of debris except in these patients.”

Obviously something—a virus or some kind of toxin—was killing cells in the Tahoe sufferers.

Wormsley was struck by another phenomenon. In order to successfully perform the kappa/lambda test, she needed a sizable population of B-cells in her samples.

“Right from the beginning,” she said, “these people seemed to have extremely low percentages [of B-cells], sometimes only one percent or two percent of their white blood cell population instead of the eight to twelve percent that we normally see. I noticed it because with a normal person, ten milliliters of blood gives you plenty of cells to do the entire assay. But I wasn’t able to get enough B-cells to feel comfortable with Paul’s patients. The background-noise level was almost at the same level as the positive cells. Again, we just didn’t see that in a lot of our other patients, and certainly not in our normals.”

Wormsley was perplexed. Here was a so-called Epstein-Barr virus disease, but the sufferers had lost their B-cells. One would expect the opposite, a profusion of B-cells, since EBV “immortalizes” B-cells. (In acute-phase mononucleosis, B-cell counts explode.) Yet three of the first five Tahoe patients tested had no B-cells at all, a finding that was repeated on additional tests. “It was curious,” Wormsley said.

She discovered another immune system disorder that was possibly related to the B-cell deficiency that Cheney's patients suffered. Several Tahoe victims had abnormally low levels of several classes of immunoglobulins, immune system proteins produced by B-cells that act as antibodies.

"If you add that into all of the other abnormalities," Wormsley said, "then the number or percentage of the abnormalities goes up even higher than twenty-five percent."

One of the most striking immunological aberrations Wormsley observed, however, was abnormal ratios of T-cell subsets. T-cells are a major category of immune system cell; they regulate production of disease-fighting antibodies. Two primary T-cell subsets are "helper" and "suppressor" T-cells, which boost and suppress antibody production, respectively. In AIDS the normal ratio tends to be dramatically skewed in favor of suppressors. Since this finding is virtually diagnostic of AIDS, Cheney and Peterson were curious to know the T-cell subset profile in the Tahoe malady.

Wormsley's results showed that four of five Tahoe patients did have abnormal helper-suppressor ratios. But, unlike the ratios in AIDS sufferers, they were low in the numbers of suppressor cells. Instead of one-to-two or one-to-three, which are typical of healthy people, the Incline patients had helper-suppressor ratios of five-to-one, ten-to-one, and higher. It was the mirror image of AIDS.

Cheney and Peterson decided to run all five samples again; the results were identical. Then they expanded the test to include more people. Approximately half of the twenty additional patients were found to have abnormally low ratios of suppressor cells to helper cells. When they searched the medical literature for other diseases that produced similar inverse ratios of T-cells, they discovered that the finding had not been reported before. Researchers had observed elevated ratios in certain autoimmune diseases such as multiple sclerosis and lupus, but always the elevation was due to an increase in the helper cell population, as in AIDS, rather than a decrease in suppressors.

The finding continued to be unique to the disease as the years passed. Said one virologist, some time later, "There is not another disease that mimics this, except perhaps some relatively rare T-cell lymphomas. But you could practice your whole life and never see a T-cell lymphoma."

Peterson and Cheney began using the curious helper-suppressor ratio as yet another laboratory abnormality—in addition to the abnormal Epstein-Barr virus antibody profile—to support their diagnosis of the disease. It was a fragile strand, they knew, and they were uncertain of its significance. Yet it was real, and it was not normal.



During one late-November after-hours session, Cheney and Peterson tried to extract a manageable hypothesis from the immensely complex events under way in their region of Nevada. Something—agent X—was being transmitted from person to person within their community, and perhaps in many communities, if the letters in their overstuffed correspondence files were to be believed. Agent X appeared to target the human immune system, in rare cases undermining the body's ability to ward off cancers but more frequently fomenting a relentless illness char-