So many medical stories begin when the patient arrives at the doctor’s office or the hospital. The doctor enters the room, and the patient begins the narrative that will determine a diagnosis and treatment. But as hospitalists, we see patients with their stories already unfolding. Someone already made a diagnosis, or at least obtained preliminary information to get us to that point. That affords hospitalists a degree of certainty that can be reassuring to some, frustrating to others. But what happens when the patient arrives and no one knows the answers? What do we do in the face of uncertainty?

The Nameless Patient

Our nameless patient arrived carrying a folder full of diagnostic statements, pathology reports, and a couple of compact discs with radiologic images. She was 14 years old, thin, and had dark circles under her eyes. “She has not been sleeping well,” her mother said, “the fevers keep her up at all times of the night.” The mother also looked exhausted, sharing her daughter’s dark circles of sleeplessness.

Our patient had fevers for almost 3 weeks, sometimes with temperatures as high as 106°F, intermittently feeling sick and acting normally, with symptoms appearing and disappearing almost as quickly: leg aches, a rash, lethargy, and swollen lymph nodes.

She stayed in the hospital for about 10 days. During the hospitalization, her blood counts, electrolytes, endocrine studies, plain x-rays, computed tomography scans, and magnetic resonance imaging scans were all normal. A bone marrow aspiration revealed no malignancy. A lymph node biopsy showed normal lymphatic tissue. When one of the specialists recommended a full body positive emitron tomography scan, the mom requested we discharge them so she could obtain a second opinion.

By then, our patient had completed several treatments, including antibiotics, for potential diagnosis. Clinicians use such abductive thinking,1 in which a “backward flow” of directly related hypotheses helps identify the origin of a problem, when the diagnostic process is not clear. While saying “we’ll use this, which usually works for X condition, and, if it works, then the patient probably has X” may help narrow down the differential list, it is not as reassuring to the patient or the family. To them, it feels like we are experimenting, that in lieu of a definitive diagnosis, we are fumbling in the dark for a possible explanation.

Inevitably, the unknowing begets dissatisfaction. They left the same way they came, with their folder of medical information a little heavier this time. We kept
pointing out to the mother that the girl’s fever curve was coming down, that something we did might be helping. But that was not an answer, only an observation couched with more uncertainty. The origin of the fever was still unknown. “They were not mad at us,” the nurses said, “they were just tired and frustrated.”

**Fever of Unknown Origin**

A diagnosis is a baptism, a naming of the signs and symptoms into a single entity that leads to appropriate treatment. Fever of unknown origin (FUO) is an un-naming, a fancy placeholder in our ever-present search for evidence-based precepts to guide our daily medical lives. To diagnose an FUO is to name the unknown, and by default, acknowledging the existence of the unknown. There are many recommendations to deal with patients with FUO, but the “guidelines” are affected by the circumstances surrounding the case, by the familiarity of the clinician with obscure rheumatologic and infectious conditions, or by the lack of clear epidemiologic data on rare diseases. Of all the diagnostic dilemmas in medicine, the patient with FUO appears as the antithesis of evidence-based medicine.

The diagnosis was originally called “fever of unexplained origin” by the authors of the seminal modern article on the subject Robert Pedersdorf and Paul Beeson, who pointed out that “(F.U.O.)...is likely to be a source of perplexity and frustration to the physicians, and for the patient the discomforts of illness are compounded by the anxiety of uncertainty.” By calling its origin “unexplained,” Pedersdorf and Beeson acknowledged that the cause of the fever was still out there ready to be discovered with a bit of effort. By calling it “unknown,” the possibility exists of never finding out the source.

One of the criteria established by Petersdorf and Beeson for the diagnosis of FUO included “diagnosis uncertain after 1 week of study in hospital.” In other words, when the patient arrives, she has no diagnosis; when she leaves, she has one, albeit one that does not confer the prognostic near certainties of others, what has been called “the palpable outcomes” of our field. While the patient leaves searching for more explanations, “wander[ing] from hospital to hospital, repeatedly enduring the same questions, the same examinations, the same laboratory tests,” we are left with uncertain feelings ourselves. Did we fail? Could we have done better? So many stories end when the doctor smiles in triumph over illness, or with tears at a perceived failure because of human limitations. When a patient with an FUO leaves, what do we feel?

**Uncertainty**

Uncertainty causes anxiety. Patients come to us with the expectation that our education and experience provide us with a glimpse of things to come. Our training puts us through a rigorous boot camp of intellectual rigor during which we deal with the common and the obscure, with simple illnesses and their complications, with rare diseases and their common manifestations. We come out at the other end thinking we have mastered worlds of scientific knowledge in the span of a few years. But one of the certainties of medicine is that it always changes, and that the truths that you hold so dearly at one point become the outmoded, outdated, and arcane way of doing things in the future. Nothing in medicine is 100%, I tell my patients when they ask me about certainties, just as nothing in life is.

So what our patients want is not certainty, because they know it does not exist in medicine. After all, they watch the medical dramas on television, and search the Internet for information about mysterious illnesses. Patients know we are human, and they know that being human means having limits to our knowledge.

Then what do they want? They want certainty to the best of our knowledge, as close to certainty as we can give. They want someone who sits down and acknowledges that there are gaps in our knowledge, that there are no absolutes in medicine, that things change from one day to the next and that the diseases we learn about from books and case studies sometimes do not behave the same way in real life.

They want to know when we do not have all the answers; and they want to know that we will try to look for them.

**The End is the Naming**

At the end of their study, Petersdorf and Beeson make a series of “tentative conclusions,” as if to conclude anything about such a nebulous diagnosis was in itself folly. They point out that most cases of FUO are common manifestations of common conditions and not unusual diseases; that delays in diagnosis can happen with the inappropriate use of already available information; and that attempts to obtain tissue samples for pathologic studies were sometimes unnecessarily
delayed, particularly in the presence of enlarged organs and masses. They also advocate the use of therapeutic trials, but only after “rational methods of diagnosis have been tried.” In other words, they find that the potential for establishing the known about a patient with FUO is pretty high, if only we apply ourselves in our search.

The diagnosis comes at the end, but it is not the end. Rather, the naming of a diagnosis, just like a baptism, is the beginning of something else. The naming of FUO, with its inevitable unknowingness, leads to further searches, until the fever, either by treatment or by tincture of time, eventually goes away. Or the actual malady manifests itself, and the diagnosis changes, from something of near uncertainty, to something for which we can offer as much certainty as we can.

If that happens, we sigh in relief that we may have an answer. Maybe. The uncertainty continues until “only time will tell.” Sometimes the newly uncovered answer, the no-longer-unknown origin of the fever, causes more anxiety for the patient than the terrible uncertainty of an FUO. Sometimes, uncertainty is a blessed relief.

References