Editorial

The Diagnosis of Exclusion

An Ongoing Uncertainty

Anybody can treat, but
not anybody can diagnose.[1]

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Four years ago, I attended a particularly memorable clinicopathologic conference (CPC). The case itself taught me a lot, but it also stimulated me to teach myself even more. What I learned prompts this editorial.

Case Summary. A 27-year-old white woman presented with a 7-year history of recurrent episodes characterized by fever up to 103 °F; pain, stiffness, and occasional swelling of her knees, elbows, wrists, and metacarpophalangeal joints; and a patchy, mottled, slightly scaly, non-indurated, violaceous rash over her trunk and extremities. The episodes would come on rapidly, persist for 3 to 4 weeks, and resolve spontaneously without residua. Testing for myriad disorders—benign and malignant, infectious, and rheumatic—all gave normal, negative, or nonspecific results.

Faced with that strange and challenging story, the discussant considered many diagnostic possibilities. Then, in a brilliant display of deductive reasoning, he systematically eliminated all but one of them, settling on adult-onset Still's disease as the diagnosis of exclusion (DOE). His presentation seemed so complete and so convincing that no one in the audience took issue with anything he said or offered any additional consideration. Nevertheless, his diagnosis was wrong. To everyone's surprise, a skin biopsy showed perineural, noncaseating, granulomatous inflammation. Ziehl-Neelsen staining of the specimen was negative, but a Fite-Faraco stain revealed clusters of acid-fast organisms in the dermis. These findings[2] are diagnostic of leprosy (Hansen's disease), multibacillary type.[3] At that point, the patient indicated that she had lived in south Texas all of her life and had never knowingly been exposed to persons with leprosy or to armadillos,[4] the zoonotic reservoir.

Comment. No one associated with this case—the primary physicians, consultants, CPC discussant, or CPC attendees—had considered leprosy in the differential diagnosis. That oversight is understandable, however, because leprosy in this country is distinctly uncommon, especially in native-born Americans. Consequently, its diverse cutaneous[5] and rheumatic[6,7] manifestations are easily mistaken for those of more frequent disorders. And in countries where leprosy is not so uncommon, it still eludes early recognition on occasion. My targeted search, for example, uncovered 3 individuals with leprosy—1 from Sri Lanka,[8] 1 from India,[9] and 1 from Saudi Arabia[10]—who, like the patient in the CPC, were thought initially to have adult-onset Still's disease.

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Another important aspect of that conference—the DOE—drew virtually no attention, despite the fact that the discussant's seemingly indisputable DOE proved to be wrong. I came away wanting and needing to know more about that type of diagnosis. Specifically, how important and common is it? Does it have an exact definition? And what about its risks and its reliability?

For answers, I turned to my personal library and reprint file and then to the medical literature at large. Altogether, I found and reviewed 20 acceptable articles on the subject,[11-30] all but 3 of which[28-30] had "diagnosis of exclusion" in their title. They crossed 10 specialties and covered the following 19 disorders: adult-onset Still's disease,[11] panic attack,[12] diastolic heart failure,[13] takotsubo cardiomyopathy in liver-transplant patients,[14] Bell's palsy,[15] anorexia tardive,[16] phantom tooth pain,[17] Alzheimer's disease,[18] nonfatal

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amniotic fluid embolism,[19] hysterical stridor,[20] primary angiitis of the central nervous system,[21,22] functional vision loss,[23] irritable bowel syndrome,[24] psychogenic cough,[25] hypertensive encephalopathy,[26] chronic bronchitis,[27] pyoderma gangrenosum,[28] trochanteric bursitis,[29] and chronic idiopathic angioedema–urticaria.[30] Although additional pertinent material undoubtedly exists, these articles were enough to convince me that a DOE is definitely important and relatively common.

There isn't, to date, an exact definition. The relevant literature consistently specifies or implies that a DOE is simply the diagnosis that remains after all other differential possibilities have been excluded. While accurate to a degree, that definition doesn't distinguish a DOE from any other diagnosis that we ordinarily make by means of essentially the same approach. So to clarify the issue in my own mind, I reexamined the information at my disposal. I concluded that the issue is more than a matter of semantics, because a DOE differs in a way that deserves delineation and emphasis.

Ordinarily, diagnoses are verifiable on the basis of distinctive symptoms, signs, test results, histopathologic changes, or combinations thereof. In that light, some disorders reported as DOEs are basically no different from any other diagnosis, because they, too, are verifiable. But the verification, for example, by brain biopsy in Alzheimer's disease[18] or by leptomeningeal biopsy in primary angiitis of the central nervous system,[21,22] is deferred for various reasons. In addition, specific echocardiographic findings can establish diastolic heart failure,[31] and characteristic coronary and ventricular angiographic abnormalities can verify takotsubo cardiomyopathy.[32]

The true DOE should be defined as the diagnosis that rests solely on clinical grounds, with no means of objective proof. By that definition, the DOE becomes nothing more than an ongoing educated guess. Most of the disorders listed above fit this definition well, the prototypical example being adult-onset Still's disease.[11]

Finally, I'd like to say a word about the risks and reliability of the DOE. Because of its uncertainty, the true DOE is always risky. Attention to key points, however, can decrease the risks and increase the reliability.

1) Include all possibilities in your diagnostic considerations. This, of course, will depend entirely on your level of knowledge. But since none of us knows everything, all of us are constantly vulnerable to making mistakes, sometimes major ones. In the CPC case presented earlier, omitting leprosy from consideration was paramount and would have led to harmful steroid therapy, had a skin biopsy not been done.
2) Remember that temporary symptomatic improvement can occur, even when the treatment is aimed at the wrong disease.[28]
3) Be mindful that when you think you have excluded a particular diagnosis, you might not have done so.[22,28] Reappraisal of your diagnosis using close, long-term follow-up with repeated studies can sometimes yield a different diagnosis.[16,20,22,28]

Coda

The diagnosis of exclusion requires knowledge, time, and patience.[23]

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