

The Pathogen Is Gone. Why Is the Patient Still Sick?

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Abstract. Persistent symptoms after infection can result from distinct biological processes: ongoing pathogen or antigen reservoirs, immune alteration, organ injury, autonomic dysfunction, disturbed sleep or secondary complications. The resolution framework helps separate these explanations rather than assigning every case to one postinfectious mechanism.

Recovery is not the reverse of infection

Clearing a microbe and restoring full health are separate achievements. Pneumonia can resolve microbiologically while leaving damaged lung tissue; viral illness can trigger a new autoimmune process; prolonged critical illness may cause deconditioning, neuropathy or persistent neurocognitive symptoms. Some pathogens can also remain in reservoirs or reactivate. These pathways differ in their implications for diagnostic tests and treatments.

Long COVID illustrates heterogeneity

Post-acute sequelae following SARS-CoV-2 infection have prompted investigations of tissue reservoirs, persistent antigen, immune dysregulation, coagulation, autonomic changes and viral reactivation. Evidence varies by mechanism and cohort, and not every patient has the same findings. The mere presence of symptoms after a positive infection test does not reveal which pathway is operating. Neither does a negative routine viral swab exclude tissue-level antigen, but absence of proof should not be converted into a claim that hidden infection is present.

Persistent symptoms can be biologically real without one biomarker

Fatigue, exertional intolerance, pain, cognitive complaints and dysautonomia can reflect complex physiology. Some mechanisms are difficult to measure with routine clinical tools. Yet the scientific response to imperfect testing is not to dismiss symptoms or to assert a preferred mechanism from them. Good clinical reasoning combines objective findings when available, careful history, exclusion of dangerous alternatives and recognition of uncertainty.

Four distinct research questions

First, did a pathogen persist? Second, did the immune system adopt a sustained abnormal response? Third, was an organ or neural pathway structurally injured? Fourth, have secondary consequences created a maintaining loop, such as severe sleep

disruption or deconditioning? Multiple mechanisms can coexist, but the questions imply different study designs and clinical consequences. The Institute's contribution is a causal map that resists single-cause explanations.

Adverse interpretations and risks

The proposition that all postinfectious illness is a clearance failure is too broad. Antimicrobials can be lifesaving for documented persistent infection and inappropriate for conditions without it. Immunosuppression can be necessary for verified inflammation and dangerous with active infection. Aggressive exercise may worsen symptoms in some postexertional conditions. This is precisely why heterogeneous mechanisms matter.

Conclusion

A patient can remain ill after the initiating infection has resolved because the organism and its tissues have acquired new constraints. That is a plausible general pattern, but identification of the actual constraints requires disease-specific evidence, not a universal 'postviral detox' diagnosis.

Differential diagnosis cannot be bypassed

The label 'postinfectious' is useful when symptoms follow a recognizable illness, but it can obscure a new unrelated disease. Thyroid disease, medication adverse effects, anemia, sleep disorders, thromboembolic disease and mood disorders can arise during the same interval. A clear account does not presume that every new symptom is a direct continuation of the initial infection. It begins with the clinical phenotype and evaluates red flags and plausible alternatives.

Temporal association is not mechanistic identity

A patient may report that cognitive symptoms began after infection, but their current impairment could reflect sleep fragmentation, autonomic dysregulation, direct injury, medication effects or an ongoing inflammatory process. Some possibilities can be supported with established testing, while others remain research hypotheses. Patients deserve neither reflexive dismissal nor unwarranted assertions of hidden viral activity. The evidence threshold should correspond to the seriousness and risk of a proposed intervention.

Why one successful treatment cannot settle etiology

An intervention that improves sleep or autonomic symptoms may alleviate disability across several causal pathways. That benefit does not show that sleep disturbance or dysautonomia initiated the illness. Likewise, improvement during a drug trial does not automatically validate the mechanism proposed by its advocates. Mechanistic inference requires more than therapeutic response, especially when spontaneous fluctuation and multiple simultaneous changes are common.

Selected scientific reading

1. [Proal AD et al. SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 \(PASC\). Nat Immunol. 2023;24:1616–1627.](#)
2. [Netea MG et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol. 2020;20:375–388.](#)
3. [Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014;510:92–101.](#)

Editorial status: Conceptual scientific essay, not peer reviewed. Not original clinical data, a treatment protocol or medical advice. Selected readings are not a systematic review. Evidence and interpretation should be assessed independently.