

Re-Framing Long COVID as Central Nervous System Dysfunction[¶]

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Four years after the emergence of long COVID, science is little closer to understanding its cause, pathogenesis, prevention or treatment than it was at its outset. This is due in part to the lack of an explanatory hypothesis that fits the scattergram of data emerging from basic, clinical and epidemiological research. We propose a unifying hypothesis that connects a triggering viral infection to the pathogenesis and the plethora of 200 symptoms: that long COVID is a central nervous system disorder of biologic origin, provisionally named “Post-COVID CNS dysfunction (PCCD)”. As neuroscience develops, it has become increasingly evident that much of mental illness and cognitive impairment has its basis in brain structure, chemistry and function. Applying this to long COVID, we propose that its symptoms are mediated through virus-induced biological mechanisms acting on or within the CNS. Both past and future research should be combined to test the PCCD hypothesis. This can open the pathway to significant progress in prevention, care and therapeutics. A multi-sector collaborative platform—with the leadership of the federal government’s Office of Long COVID Research and Practice—could, for example, assist in testing, improving, and implementing this hypothesis.

Keywords: Long COVID; Central Nervous System; Post-COVID CNS Dysfunction

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POST ACUTE COVID-19 syndrome (PACS), generally called long-COVID, is the most widespread and damaging post-acute infectious syndrome (PAIS) in history (1).

It is also one of the most complex and protean diseases to have challenged mankind. Four years after its emergence, science is little closer to explaining its cause, pathogenesis, prevention or

treatment than it was at its outset.

A grass-roots reappraisal of our national long COVID strategy is overdue. This should start with a unifying hypothesis that can plausibly link cause, mechanism and symptoms that produce a devastation of impairment and suffering.

While the early forecasts (2) of long- COVID's toll have been strikingly accurate, the efforts to mitigate it have lagged dramatically. The recent U.S. adult prevalence is 7 percent (3) with nearly 30 percent of an estimated 17 million sufferers reporting significant activity limitations. The direct and indirect U.S. economic costs (4) are estimated at \$2.6 trillion.

The current state of science describes (5) long COVID as "a complex nonmonolithic multisystemic disease with sequelae across almost all organ systems...with many subtypes that may have different risk factors and distinct biological mechanisms that may respond differently to treatments." This umbrella definition confusingly makes it virtually impossible to differentiate what is or isn't long COVID.

Frequent leads (6) emerge from basic, clinical, and epidemiological (7) research that seek to connect the pathway from viral infection to a myriad of two hundred (8) symptoms. But while the field lacks breakthroughs, it's not lacking explanatory hypotheses that have yet to reveal promise. As the media (9) continues to portray the helpless plight of sufferers—researchers, practitioners and patient advocacy groups struggle to develop viable disease models from the growing scattergram of published data. Lack of progress is blamed on public and government disengagement (10) underinvestment (11) and misguided (12) research.

After four years the central questions that characterize long COVID have not been resolved: Is it mental, physical or both? Is it "real" or "psychosomatic"? What research approaches are likely to be productive in the near-term? Most importantly, how are sufferers most likely to be helped now and in the future as the knowledge base grows? In sum, this is not a predicament from which significant and timely medical advances emerge.

Among the many factors contributing to this disappointing lack of progress, three stand out: (i) the absence of a unifying hypothesis that explains the plethora of symptoms, (ii) the frequently contradictory disease paradigms invoked by the biomedical and patient advocacy communities, and (iii) the lack of objective diagnostic criteria for the condition.

In developing a unifying hypothesis, these three negative synergistic barriers are collectively best addressed through the recognition that long COVID is not (13) a *de novo* new condition. This is a focusing historical lens that provides key insights into the origins and trajectory of long COVID.

Diseases similar to long COVID have been recognized (14) for nearly a century. It is well-established that PAIS is caused by a variety of pathogens including viral infections (15) which can trigger chronic fatigue and cognitive impairment syndromes. In exploring the history of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), Lyme's disease, functional neurological disorder, and fibromyalgia, striking similarities with long COVID emerge. These include an onset triggered by acute infections, symptoms not amenable to validation through objective findings, vague diagnostic criteria, poorly defined clinical phenotype, significant functional impairment

and disability, pathobiologic mechanisms that have eluded researchers, no disease-modifying treatments, chronic underfunding, and unresolved societal conflict.

An illuminating overlay is that PAIS is also a "contested illness." (16). This is a formal construct in medical anthropology that has been the subject of scholarly investigation (17) since 2005, fifteen years before the appearance of long COVID. The term seeks to explain the mysterious commonalities of these disorders. It presciently describes (18) the conflicts that arise when the cause and legitimacy of chronic fatigue and cognitive impairment syndromes are disputed among traditional biomedical and self-empowered patient communities. Long COVID now perpetuates this irreconcilable struggle for epistemic authority.

What are new are the remarkable scope, scale and rapidity of spread of long COVID. This is ascribed (19) to the magnitude of the global COVID-19 pandemic and to the unprecedented amplification by contemporary digital media.

With this hindsight, we posit the unifying hypothesis that long COVID (or PACS) is a central nervous system disorder of biological origin, provisionally named "Post-COVID CNS dysfunction" (PCCD). As such, it is a new version of PAIS. This can explain long COVID's cause, pathogenesis and clinical presentation. Key aspects remain to be proven, but it merits consideration and rigorous testing. It fits the scattergram of existing evidence more closely than current alternative hypotheses.

As neuroscience develops, it has become increasingly evident that much of mental illness (20) and cognitive impairment (21) has its basis in brain structure, chemistry and function. The application of this construct has revolutionized the understanding of disparate mental illnesses such as depression, schizophrenia, PTSD, autism and dementia, among many others. Now it should be applied to long COVID.

The neurobiology (22) of long COVID has been comprehensively reviewed. While direct brain infection is thought to be an unlikely mechanism for the neurologic and neuropsychological sequelae of COVID-19, at least six other pathobiologic mechanisms (23) including immune dysregulation, (24) have been postulated to account for neural injury. Infectious and immune challenges can cause neuroinflammation and CNS dysfunction. Recent studies involving PAIS-type condition fibromyalgia (25) and ME/CFS (26) reveal CNS, phenotypic and immune profiling findings consistent with the pathophysiology of the PCCD hypothesis. This can explain long COVID cognitive impairment ("brain fog") and neuropsychological symptoms (e.g., sleep disturbance, PTSD, anxiety and depression). While the attribution of neuropsychiatric symptoms to CNS dysfunction is generally accepted, its extension to long COVID's systemic, gastrointestinal, cardiopulmonary and endocrine symptoms is less clear (27).

Historically, long COVID's heterogeneous symptoms have been sorted into a number of categories aligned with traditional organ-system oriented medical specialties. The PCCD model postulates that these symptoms may all be mediated through biological mechanisms acting on or within the CNS. This may occur through disparate pathways directly (28) through virus-induced biological mechanisms, or indirectly through pandemic-associated social and environmental determinants (29) of health. Psychological distress (30) at all stages

of COVID-19 infection has been associated with increased risk of self-reported long COVID symptoms. Moreover, psychological, cognitive and neuropsychiatric symptoms that result from overwhelming stressful experiences are accompanied by observable pathophysiological changes (31) in brain function. The PCCD model provides a holistic view of causation through both direct viral and indirect physiologic mental stressor mechanisms that converge to result in CNS biological dysfunction.

PCCD obeys a cardinal principle in clinical medicine: namely to seek a single unifying diagnosis (32) that explains all the patient's signs and symptoms, rather than to rely on multiple causes. For example, migraine (33) headaches can present with a broad spectrum of intracranial and extracranial symptoms that best fit a single diagnosis. However, even with the postulate of PCCD's CNS origin, a multidisciplinary approach to treatment may still be indicated to address extracranial symptoms.

The second barrier to progress is the frequently irreconcilable disease paradigms invoked in the search for solutions. In separate corners are the biomedical and patient-centric ecosystems.

The biomedical paradigm relies on established professional standards in research and patient care. This encompasses study design, causal inference, diagnostic rigor and treatment efficacy. Research seeks organic associations such as biomarkers and pathobiologic mechanisms as a basis for identifying treatments. On the other hand, essential features (34) of the patient-centric paradigm include the mobilization of subjective evidence, the creation of group identity through experiential knowledge, and the co-production of knowledge with experts of the biomedical paradigm.

By invoking the PCCD model, flaws in both the traditional biomedical and patient-centric disease paradigms become evident. In both these paradigms the default clinical pathway is to search for objective signs of non-CNS organic illness targeting presenting symptoms. This channels the patient through an arduous health-care labyrinth of organ-specific specialists until a negative assessment points toward a mental health intervention. This approach satisfies neither practitioner nor patient and ends in frustration and conflict for all.

In the PCCD model, the critical change is a new default clinical pathway: that the presenting symptoms result from CNS dysfunction. Hence, the scattershot pursuit of extracranial etiologies could be largely avoided. It is indicated only when there is a high index-of-suspicion for non-CNS organic disease.

The third impediment to progress is the lack of a long COVID diagnostic case definition to guide basic and clinical research. As experts (35) of their own illness, sufferers have created an over-sensitive and highly inclusive case definition (36) to "consider the experiences of all people with COVID-19 symptoms, regardless of testing status." The resulting heterogeneous patient population does not fulfill traditional biomedical study design standards for generating valid findings. Despite extensive efforts, no valid marker has yet been identified to improve the accuracy or objectivity of the diagnosis.

To address these concerns, we suggest principles of an updated clinical case-definition that trades sensitivity for greater specificity and reliability. This approach is vital to support credible research and should not be compromised. Importantly, these

principles migrate long COVID from a patient self-diagnosed to a practitioner-diagnosed condition.

While the subjective symptom clusters and duration requirements of earlier World Health Organization (37) or Centers for Disease Control and Prevention (38) case-definitions can be retained, a number of objective requirements are added. These relate to laboratory-proven (39) evidence of SARS-CoV-2 infection, exclusion of those with non-CNS organic disease, end-organ damage from severe acute COVID-19, or evidence of malingering. This tighter case definition also excludes various forms of autonomic dysfunction (40) frequently lumped with long COVID.

Many of the precepts of PCCD are contrary to dominant paradigms and will evoke significant challenge. For example, sufferers may take exception to the putative CNS origin of the condition. Researchers, practitioners and sufferers will remain committed to investigating non-CNS pathways. Advocacy groups may not accept the notion that practitioners, not sufferers, are best positioned to make a definitive diagnosis.

PCCD directly confronts a deep sociocultural resistance to the concept of the brain as the locus of long COVID. "Mental illness" has a long and freighted history of stigmatization, patient vilification and maltreatment. It's not until recent times that changes in behavior, mood and function have been ascribed to a biological or biogenetic basis. It's not surprising that sufferers have rejected the societal distinction between the physical and the mental. In vitriolic terms, patients view this as "gaslighting" by practitioners, and as censure and disregard by the research community. Unsurprisingly, they abhor their dismissal to a stigma-laden mental disorder quagmire. The outlet for this mass frustration is the "social construction (16) of contested illness legitimacy."

Perhaps shockingly, in the twenty-first century the nature of the relationship (41) between the mind and the brain is still poorly understood. In particular, the bridging of neurosciences and clinical psychiatry in the relationship of neurobiological mechanisms and clinical mental disorders is in early development. With currently limited tools, the brain's unfathomable complexity makes the transition from basic research to the treatment of brain disorders a long-term and unpredictable endeavor. Thus, the linkage of impairment and disability of long COVID to CNS dysfunction is not the end, but the beginning of a potentially fruitful line of investigation. PCCD as a unifying hypothesis does not offer a quick fix to patient suffering. However, it can connect past with future research exploring mechanisms, prevention, care and ultimately therapeutics (42).

There is urgency to pursuing PCCD in a new framework of knowledge generation and validation. This can potentially guide more productive government investment in healthcare, research, prevention and treatment. Most importantly it may help current sufferers—as society gradually converges in how it thinks about long COVID.

The productivity of this endeavor is dependent on an enabling collaborative culture that serves the interests of diverse constituencies. It will require a new common ground of goodwill, and national institutional collaboration. The U.S. Department of Health and Human Services has created such a platform by establishing The Office of Long COVID Research and Prac-

tice in 2023 (43). This office has stood up the Federal Advisory Committee on Long COVID, which “through collaboration with federal partners, researchers, clinicians, patient advocacy organizations, and the business sector.....[will] continue to make

progress toward America’s most urgent calls-to-action.” (44)

Long COVID sufferers and society have much at stake in the success of this and other similar collaborations. ■

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