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LETTER TO THE EDITOR

Fibrinaloid microclots in long COVID: assessing the actual evidence properly

We have read with interest an opinion piece [1] on fibrinaloid microclots in the plasma of patients with long COVID and related diseases.

In the article by Hunt et al. [1], the authors first claim that "We initially critically appraised the research studies that had led to demand for apheresis treatment" (citing their Cochrane review). We wish to point out that several of the authors of that paper and one of its reviewers (Carson) are now authors of the article by Hunt et al. [1], while Garner is a Cochrane Editor. Cochrane has thus far refused to append an online comment, where we point out erroneous facts (however, the rebuttal can be found at http://dbkgroup.org/dealing-with-clots/). Repeating erroneous facts, when the authors know them to have been rebutted, is poor practice.

Hunt et al. [1] then claim to "describe the development of the {microclot} theory," a claim that unfortunately bears no relation to the true version but rather represents their opinion of the theory. Readers might instead imagine that those of us who actually did develop the theory might be best placed to discuss its development accurately. The microclot theory is airily described as "arising from a research team in South Africa" when in fact the joint program led by Pretorius and Kell is of over 10 years duration and has produced more than 60 joint peer-reviewed publications.

We also wish to point out the comment "We conclude the inferences for the hypothesis are not based on evidence…." We are not quite sure if the authors suggest that there are no such entities as microclots (ie, that we made it up), whether they do not believe that microclots have an amyloid nature, or if they are indeed upset that we call the entities "microclots." Our first definition of the term "microclots" in the article by Pretorius et al. [2] was given as anomalous (amyloid) deposits (microclots).

As with all new discoveries, there might be different opinions. Rather than sitting on the side line and writing opinion pieces, we should rather come together as researchers to determine the nature and content (by further robust experimental design) of this novel entity and in fact debate the terminology to be used if there are disagreements.

Pretorius et al. had long noticed that blood could clot into a highly anomalous form, using measurements from the electron microscope, including (with Kell) the effects of unliganded iron. At this time, these anomalous clots were referred to as "dense matted deposits." The discovery that they were actually amyloid in nature and could be induced by tiny amounts of bacterial cell wall material [3,4] led to the ability to make measurements in a far more high-throughput manner using fluorogenic stains such as thioflavin T and the Amytracker dyes. We also observed the microclots in a large number of chronic inflammatory diseases, each of which has an infectious origin. The amyloid nature of these clots explained striaghtforwardly their resistance to fibrinolysis [5,6].

It was obvious from the earliest times that acute COVID involves coagulopathies, and we discovered the existence of extensive microclots that stained with amyloid stains in the plasma of sufferers. Measurements of microclots in sufferers from long COVID also showed a far higher prevalence of microclots in their plasma than was observed in that of the controls [2,7–9], although the later arrival of vaccines containing or inducing spike protein added nuance. We showed that the spike protein alone (as with bacterial cell wall components) was able to induce the amyloidogenic microclots in normal plasma [10] and that the extent of these fibrinaloid microclots was correlated with the virulence of the variant; this latter observation provides an important control or indication that the microclots are actually on the disease pathway. The amyloidogenic nature of the spike protein is itself also well established, (as shown by Pretorius and Kell) and recently confirmed by Ryu and coworkers who also confirmed the pathological nature of fibrin in Long COVID [11].

In addition, note that the roles of fibrin amyloid microclots in disseminated intravascular coagulation (odds ratio = 51) and mortality in intensive-care patients (odds ratio = 5.4) have been determined by the Toh group [12]. Various studies have also shown the existence of fibrin inside the clots (along with many other proteins), so they are correctly referred to as (micro)clots.

While the initial discovery of amyloid-containing microclots [3] was hypothesis-based, the "microclot theory" is thoroughly grounded in very extensive experimental evidence, even if the study by Hunt

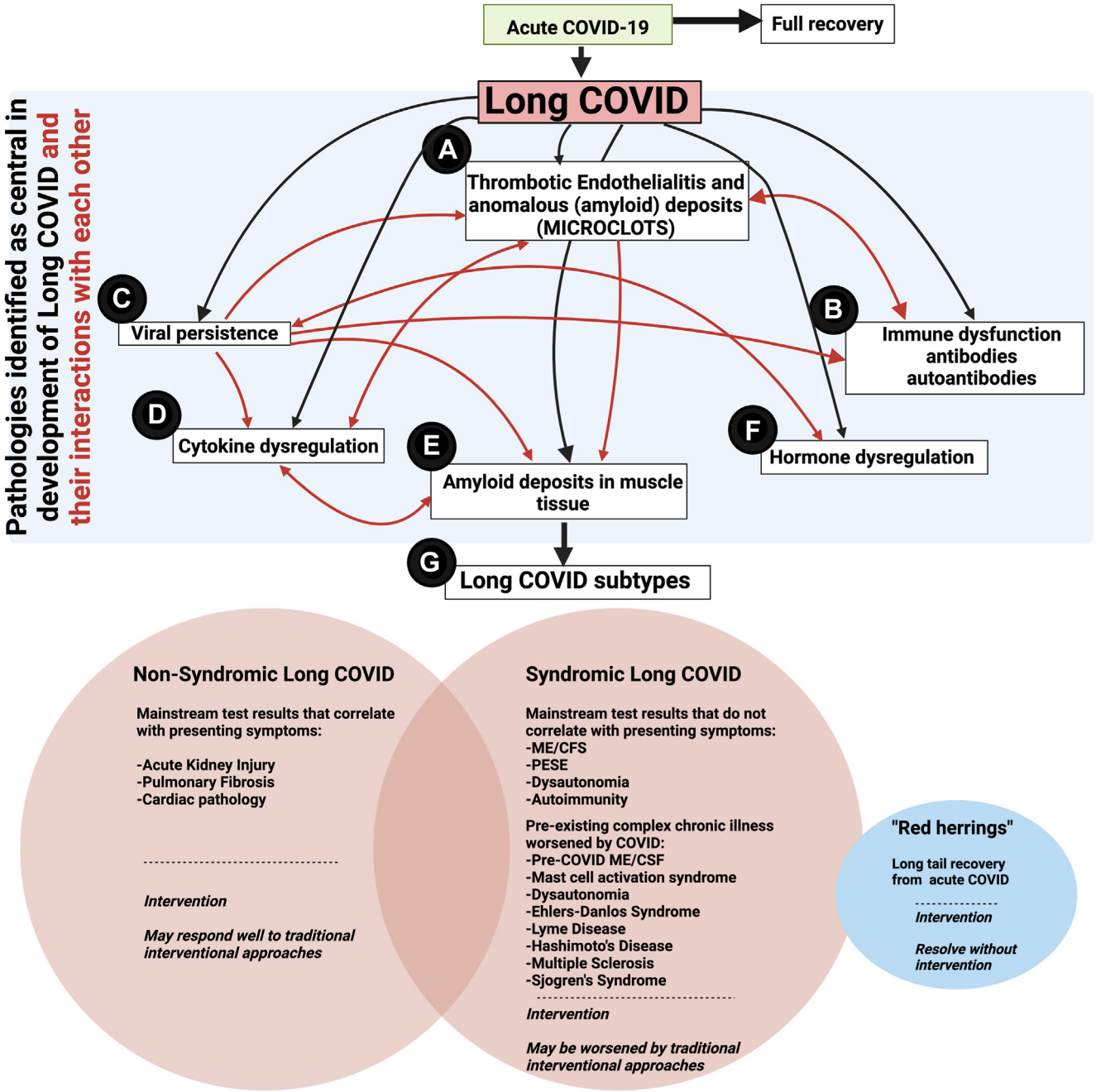

FIGURE An overview figure showing the key pathologies (black arrows) involved in the long COVID as well as their interactions with each other (red arrows). (A) Thrombotic endothelialitis and anomalous (amyloid) deposits (microclots) (as per our first definition in the article by Pretorius et al. [2]), (B) immune dysfunction and autoantibodies, (C) viral persistence, (D) cytokine dysregulation, (E) muscle involvement, (F) hormone dysregulation, and (G) subtypes of long COVID as a result of the key pathologies driving the symptoms. ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; PESE, post-exertional symptom exacerbation. Created using Biorender.com.

et al. [1] chooses to ignore it. The risible claim [1] "we conclude {that} the inferences for the hypothesis are not based on evidence…" thus does not sit easily with the facts—and facts that are, after all, very easily checkable by those who wish to (Figure).

AUTHOR CONTRIBUTIONS

DBK, EP, and MAK equally contributed in the writing and editing of this paper.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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