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THE PANDEMIC`S UNRESOLVED INFECTIOUS PSYCHO-NEURO-IMMUNOLOGIES: MYELOID CELLS, VESSELS, NASAL CROSS-ROADS

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SUMMARY

Unresolved infectious psycho-neuro-endocrino-inflammation (PNEI) denotes an area of tragically accelerated interest because of SARS-CoV-2`s capacity to meddle with the immune responses in a stage-wise fashion. Its pandemic, interacting with antecedent further deteriorating health and living conditions, takes a direct toll of million human lives. In order to withstand the plethora of slowly or never easing ailments labeled "Post-acute Sequelae of Covid-19 (PASC)" a comprehensive understanding from the intrusions up to its emerging aftermaths is paramount. For the strained health professions these prospect care requirements of 1 in 5 for a non-convalescence overlapping also with other tedious long-hauling "triggered" disorders adjacent to psychiatry like chronic fatigue with orthostasis intolerance or intracranial hypertension (ME/CFS-OI; IIH). For the lattter two new pathophysiologies are proposed in order to inform a strong rehabilitative psychiatric liaison not referring sufferers to a psychiatric "enigmo-somatic bin", but to an invigorated somato-psychic care e. g. for exertional malaise. Starting from early stimulation of escalating myeloid-derived suppressor cells the neglected mast cells show up (for now without their lymphatic partners) as ambivalent core participants. They interact or orchestrate or sequentially explode in etosis guarding or breaking sane barriers especially at cerebral arteries. In Covid-19 they seem unleashed at the blood-brain-barrier by the early virally invaded nasal ganglia, which plausibly mis-direct the quickest interstitial arterio-intramural outflow – thus a.) losing its ability to "comply" with pulsatile flow through varying the width of its sliding chambers causing ME/CFS-Orthostatic Intolerance and b.) inflaming and stiffening the brain's interstitium through a "push-back" outpacing the confuted inventive "glymphatic-1.0" model. Mast cells – colonized or not – plausibly permeabilize the choroid plexus and venous or bony brain barriers co-causing the not so rare Idiopathic Intracranial Hypertension. Innate memory - as activated by short RNAs through BCG-vaccinations directed against the permanent TBC-pandemic leads to hopes for a hastening of resolutions through a combined medical, exertional, psychosocial, and psychiatric rehabilitation informed by a new "PNEI" – paving the way for amplified-BCG or future psychiatric vaccinations.

Key words: *SARS-CoV-2 – PASC – PNEI – ME/CFS – orthostasis intolerance – IIH – PPG – mast cells*

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INTRODUCTION

"The truth is rarely pure and never simple."
Oscar Wilde

Here we present a cross-over from a broad-based attempt to come to grips with the pandemic's long-term challenges in order to better delimit the role of mental health care. Most references are omitted but can be retrieved on a preprint (with DOI-names at www.biposuisse.ch/Perugia), while a full paper is to be published this year.

After the still sweeping defeat: reconstruct and prevent better

Mental health publications quickly dealt with Covid-19 psychologically, while "neuropsychiatric" trails below 4% and global mental health - as crucial as neglected (Adhanom Ghebreyesus 2020) - crawls. Large efforts from its workforce shall increase agency under "climatic" crises (Ripple 2020, Lynas 2020) – which abysmally decrease prospects for the young. The Covid-19-pandemic resulted as much from societal short-comings (Casesmeiro Roger 2021) as from the SARS-CoV-2` immune subversion especially of the, often too resilient – but "*Do-Not-Resuscitate!"*- hampered (Alhatem 2020, Sutton 2020) – elderly (Levin 2020).

Psycho-Neuro-Endocrino-Immunology (PNEI) covers, also infectious, bio-psycho-social resilience to "stress" (Peters 2021). To understand Post-acute Sequelae of Covid-19 (PASC) "unresolved infectious PNEI" – involving neuro-interacting (Xu 2020, Selye 1965) mast cells (MCs) - proves essential (Bonneau 2007) (Table 1).

How the pandemic takes inequalities further

SARS-2- seropositivity or anxio-depression in "lock-down" were best predicted by *prior* traumatic life events - besides male sex, smoking, family case(s) or autoimmunity. SARS-CoV-2 (SARS-2) targets patients who are: aged, obese, mentally ill, socio-economically, ecologically (H. Wu 2020) threatened, devoid of access to and/or providing health-care themselves (Bryant-Genevier 2021, Salazar de Pablo 2020) and, milder, expecting mothers – conditioning offspring (Lins, 2021) – and rarely children as multi-system-"MIS-C".

"Long" Covid-19 - never to end?

While knowledge follows the surge of vaccines, carers fear the "#long-Covid-19" "for years to come". Such after-effects persisting beyond 2 months (Nalbandian 2021) are ascribed variously to: A. the *infection itself* (in- and outside the brain with its immune- thrombotic

Table 1. Psycho-social and biological stresses derail various neuro-immune responses

STRESS	**Resilient Stress & Immune Response**					**Maladaptive Stress & Immune Response**			
Responder	**SYMP**	**PSymp**	**HPA**	**N**-peptid / N-troph	Persistent excessive Strains ↑ STRESS Response	**SYMP**	**PSymp**	**HPA**	**N** -peptid / N-troph
Tr.mitter	NA/ADR	ACh	Cortisol (↑ CUS)			NA/ADR ↓ TJbarrier	ACh	Cortisol	
CNS	Constructive = positive MOOD					Destructive = negative MOOD			
BODY	Staged balances of BARRIERS, homeostases, IR-cells responses, repair ➔ RESOLUTION					Derailments: at BARRIERS, of homeostases, IR-cell responses, repair ➔ NON-RESOLUTION			
MCs	CNS-arteries: Abluminal, tonically inhibited					MCET, CK-crumbs➔LYMPH-NODE activation			
LYMPH	Isolation of inflammatory cauldron					Neural opening of LYMPHATICS. MC egress.			
SARS-2	Elimination					Entries / Sanctuaries ➔ Spreading.			

Modified after Fig. 2 (Peters et al., 2021). SYMP vs. PSymp: sympathetic versus Parasympathetic system; HPA: hypothalamic-pituitary-adrenal axis; CUS: Chronic Unpredictable Stress; ACh: Acetyl-Choline; NA/ADR: Nor-Adrenalin; NKcell: innate NAtrual Killer cells; TH1/TH2: T-helper cells type 1 or 2; Treg: regulating T-cells; N-peptid / N-troph: Neuropeptides, Neurotrophins; INFγ: Interferon γ; IR: Immune Response; TJ-barrier: Tight junctions "gluing" barriers.

response), B. its *initially or subsequently* triggered *immuno-pathogenetic (viral)-stress cascades*, C. less to *primary* neuro-psychiatric microbial lesions and epi-genetics, D. to what severe *psycho-social stress* damaged: loneliness preventing some substance-abuse and obesity increasing Covid-19-mortality, in contrast to mental illnesses. These seemingly secondary long-term mental health stresses induced many to abandon healthy habits and equitable ratiocination, dishearteningly increasing vaccination hesitancy.

THE COVID-19-PANDEMIC FROM SARS-COV-2: A RAPID SURVEY

By imperfect testing (Rhoads & Pinsky 2021) SARS-2 was reported from Italian sewage weeks (La Rosa 2021, Fongaro 2021) and from serologies months (Apolone 2020, Chossegros 2020) before the "first" case. Covid-19 proved much faster-spreading: rapidly exceeding the predecessors' (mental) services' loads (Szcześniak 2020).

Straight from hell?

The closest relative SARS-CoV-1 (SARS-1) had been recovered in 2013 by the same "WIV", Wuhan Institute of Virology, (Hu 2017) from interferon-"stuffed" bats, motivating an admonishment to prevent: a) further pandemics – as before when H1N1-influenza leaked from a Chinese (Wertheim 2010) or SARS-1 repeatedly from East-Asian labs - and b) the dangers of "gain-of-function" (in species-specific contagiousness) research (Cyranoski 2017). The latter was nevertheless pursued at WIV through international funding and now refers to the Swiss ABC-lab (Williams 2021). Already the surprisingly simultaneous mutations leading to Covid-19 – close to bats` SARS by sequence, and to pangolins` SARS by binding domain – could have been engineered by insertion of a novel furin site (Segreto & Deigin 2021). Albeit this might not have occurred (Cyranoski 2020, Kramer 2021), the future tempting power and the hazards (Weiss 2015) exerted by such engineered mutations are gigantic, whereas their original motivation (since before 2000) has become obsolete by vaccinology's speed-up. By another lab early Covid-19-patients from the animal-selling market received first-aid (Huang 2020). The spread within most countries was weakly opposed because of a puzzling lack of perception of the long persistence of PVJ- but not chlorhexidine-sensitive SARS-2 (Peletier 2021, Davies 2021, Shewale & Ratcliff 2021) on nasal and tongue mucosae, on shoes and malls, and on UV-sensitive conversational micro-drops filterable by non-sterile masks (Howard 2021).

COMING TO KNOW THE COVID-19-DISEASES BY THE CLEVER SARS-COV-2

Covid-19 presents as a lung-focused, yet generalized (micro-)-thrombotic disease involving all organs - whereby thrombi conform to arterial walls (Fahmy 2021). All this and a "misfiring" pro-inflammatory cytokine (PIC) "storm" (here PICKS) seemingly takes origin from a "emergency myelopoiesis" within bone-marrow whereby persistently stimulated special neutrophils and monocytes (Veglia 2021) exert potent immuno-suppressive, but also health-promoting, activities as myeloid-derived suppressor cells (MDSCs), which in Covid-19 disrupt NKcell and T-cells, but not B-cells. MCs augment various MDSC-activities.

Table 2. Human CoV-Variants: Escalating to ARDS, persisting in chronic aftermaths

Human ARDS & Coronavirus Diseases: gradation and temporal dynamics.					
Disease:	**Initial**	**Advanced**	**Severe**	**CNS / LC-19**	Sources
ARDS {↗ miRNA-146a miRNA-155}	Into Pneumo-cytes II: PICs	Mϕ: PICs damage EC	Alveol. flooding PMNs	[Delirium] (Psych. GAD MDD) fibrosis	Rabaan 2020 Badraoui 2020 [Kalra 2021] Y Guo 2008 (Liu 2021) Zubair 2021 {Y Han 2016}
MERS via DPP4 1000 by 903 d	Fever, Throat	Chest pain *stroke, GBS Bickerstaff, encephalitis*	ARDS Chest pain		
SARS-1 1000 by 130 d	Myalgia, Gut Headache	*encephalitis, stroke, GBS*	ARDS ➔ neurons glia		
Covid-19 via ACE2 x **clathrin** 1000 by 48 d	Fever, Cough Dyspnoea. Gut, Myalgia [eos🡻]	Chorioid plexus: SARS+ *Trv.myelitis, DM AC-4*	ARDS		ISARIC 2021 [Outh 2021]
Covid-19 (H): CNS	Anosmia 48%	Anosmia ➔ 🡾 7%	30% :SubArach-noid bleeding; 10% Stroke	Uncoord. 3/4 Paresis 1/2	Ermis 2021
Covid-19 (+3m)		**GM**: ↗ OLFCX, **R&L_**HC, INS, HESCH, **L_**OPERC, **R_**GCING [**corr.** 🡾 Memory] **WM**: 🡾 MD, 🡾 AD, 🡾RD, ↗FA	Sleep 2/3, Fear 1/2 PTSD 40%, MDD 1/3 Soma.1/3 Anx 1/6		Y Lu 2020 Dong 2021
Covid-19 Asymptomatic:	↗Ribosomes ↗T-cells ↗B-cells ↗cell-killing (-)Th1-/Th17	INF-γ or classic-complemental ➔ ↗ Th17-boosting Nphs ↗↗			YH Chan 2021
	Only Envelope-E2 proteine attack pore ➔ ARDS				**B Xia 2021**
Covid-19 (H)	**↗ - ↗↗: MIP-1A, IL-7, IL-2, IP-10, G-CSF, IL-10, MCP-1, TNF-α**				C Huang 2020
Covid-19 (H)	**↗ - ↗↗: (CD14+)CD16+ monocytes rel. PICs**				
	↗ - ↗↗: CXCL9, CXCL10, CXCL11 dep on Akt				Callahan 2021
Covid-19 (H)	**IL-1α, IL-1β, IL-6, IL-10, IL-17A, IL-12 p70, IL-18, IFNα, TNF**		**IL-33, IL-16, IL-21, IL-23, IFNλ, thrombopoietin, eotaxin/-3**		C Lucas 2020
MIS-C by ADE Age: 0;1-7;0-15;0 1f:2m **1. Vaccinations** Train immunity 2. **Coinfected: <1/2** 3. immature ACE2 4. immature PICKS 5. [MC deficiency]	**Interval: 4-5 weeks** Conjunctivitis Cough (1/3) Fever (27%) **Serum+: 82%** PCR+: 1/3	**95% ➔80%: Cardiovascular** shock **90% ➔ 70%:** Gut **35% ➔70%:** Lung **60% ➔ 40%:** Skin Rashes **7%➔ 21%:** Kidney **15% ➔45%:** MAS / HLH **20% ➔7%:** CNS / PNS	ICU 1/3 ← Note: ➔: Change of prevalence from ages [0;0 – 12;0] ➔ 13;0 – 18:0].	1-2% sequelae	F Haslak 2021 Lo 2021 Q Wu 2020 [Springer 2019]

ACE2: ARDS/SCZ: ARDS in schizophrenia; DPP4: Dipeptidyl peptidase 4 receptor; ADE: Antibody-dependent Enhancement; EC: Endothelial cell. CHPLX+: Choroid plexus positive for SARS-CoV-2; CNS.vascular: Cerebrovascular; GBS: Guillain-Barré-Syndrome / Bickerstaff. GAD: Generalized Anxiety Disorder. (H): In-hospital-patients. MDD: Major Depressive Disorder.Mϕ: macrophage; MAS: Macrophage activation syndrome, HLH-like variant: HLH: "Hemophagocytic Lympho-Histiocytosis". MIS-C: Multisystem Inflammatory Syndrome-Children. PIC: Proinflammatory Cytokine; PICKS: PIC "Storm".
(Lu 2020): OLFCX: olfactory (piriformis) cortex; HC: hippocampus; INS: insula; HESCHL: Heschl's gyrus, OPERC: operculum Rolandi; GCING cingulate gyrus. GM: grey matter; WM: white matter. AD: axial diffusivity; MD: water movement; FA: fiber anisotropy.

Hereafter MCs provide the alveolar septa with antiviral PICs becoming triggered by platelets and their activation factor (PAF) – which MCs secrete unless inhibited.

PASC – beyond convalescence – instead stems from an enduring low-level inflammatory state engrafted on also other antecedents or secondary infections – overlapping with 1-in-3 post-sepsis Chronic Critical Illness.

Covid-19 – the SARS-CoV-2-disease – by mast cells?

After the first-week Covid-19-flu diversifies among 20 truly infected humans - strongly following host factors - into 3 paths of critical and 1 of severe illness, of which 2-4% perish under intensive care. Sputum correlates two-fold with mortality, the high-density ACE2 tongue and nose being the entrance area – unless PV-iodine is used (Carrouel 2021) (Table 2).

Covid-19 presents as an ARDS-prone inflammation from hyper-thrombotic and hypo-fibrinolytic events around endothelial cells (EC), their progenitors and «neighboring cells» derailing into PICKS, while early SARS-2-invasion of pneumocytes-II via macrophages (Mφs) can cause the alveolar endothelial edema of "ARDS". This pneupathy initially results from – chromoglycin-sensitive – protease-liberating degranulations of MCTCs triggered by coupling of SARS-2`s spike-RBD with ACE2 (also impeding ACE2 to moderate through angiotensin-1-7), with directly and translationally pro-inflammatory and TJ-cracking effects (Wu 2021).

Despite SARS-2` ubiquitous presence severe damage by perivascular infiltrations and viral intrusion in fact may arise only later (Remmelink 2020, Achermann 2020), when virus-infected MCs selectively recruit antiviral innate NK-cells (Portales-Cervantes 2019, Savoy & Boudreau 2019).

Better (not) be a child for once: Multisystem Inflammatory Syndrome

The respiratory ACE-2-docking points develop with age. COVID-19 is usually transient in children and PASC similarly abates. Rarely "MIS-C"-Covid-19-illness with nausea (¾), fever and shock recurs a month after the normo-pediatric rapid antibody response. MIS-C derailing via HMGB1-RAGE or by delta-hyper-replication is plausibly due to an invasion via "antibody-dependent enhancement" involving MCs (Wan 2021, Ricke 2020, 2021). IL-27-elicited MIS-C (Si 2018) (re-)damages gut (4/5), skin, conjunctivae (1/2), and the brain (40%) with pathognomonic Kawasaki-like cardiac failure (2/3), strawberry-tongue (4/5), and coronary ectasias. Its adult version causes obnubilation, dysautonomia, urticaria being treatable as an MC-activation (Theoharides & Conti 2020).

COVID-19 AND THE BRAIN

Coronaviruses (CDC) rarely cause neuro(myelo-)degeneration. 1-in-3 struck by MERS- or SARS-1 suffered delirium (28%) or common hypomania, persisting in half over months with unstable memory or mood. After the three pandemics combined moderate anxio-depression and PTSD (Boden 2021) occurred throughout months among all (1/6), quarantined or healthcare-providers (1/4), and especially the ex-recovered (40%). Yet after Covid-19 most «recover without experiencing mental illness» (Rogers 2020; Gramaglia 2021).

Acutely SARS-2 too may aim at the brain, the other (humanCoV-HKU1/ OC43 / NL63/ 229E) coronavirus' neuro-pathologies being variegate with rare pathogenic spreads "through axons" (Dubé 2018, Butler 2006). Access through the BBB is provided neither by stress (Roszkowski & Bohacek 2016, S Lee 2018) nor through maybe CSF-increasing leaks in infected organoïds (Pellegrini 2021), nor through the naso-intestinal (Cataldi 2020) or olfactory path (Butowt 2021) - reaching unconnected parenchyma in hACE2-mice "through VR-spaces" (Cheng 2020) - perhaps if used by MCs.

Cerebral Covid-19: symptoms, clinical imaging, and pathology

Neuro(-psychiatric) acute Covid-19 (Rogers 2021) presents with anosmia/dysgeusia (40%) – which are *half* as common in severe Covid-19 (Purja 2021) – and aching fatigue, with rare anxio-depression - acute encephalitis being relegated to sepsis (Tong 2021). Brain-imaging remains blind in 40% to multi-scale subcortical, meningeal, or white matter disturbances, with thrombo-vasospastically compromised cortical, yet high cerebellar perfusion. While neuro-diseases are rare, immune-pathology can follow mild Covid-19. Post-mortem microglia interacting with often infiltrated NK-cells appears altered, "profound nodules" denoting mild encephalitis. Non-destructive Covid-19 neuro-spectrum overall spares the frontal lobes, destruction requiring more, external, insults (Matschke 2020).

What opens the blood-brain-barrier first in Covid-19? Mast cells?

A tough barrier to understanding remains the "cracking" of the initially sane blood-brain-barrier (BBB), normally only traversable for MCs, which "despite their small number activate all components of the neurovascular unit" (Silver & Curley 2013, Traina et al. 2017). Because late PICKS will *not* explain the commonly early neuropsychiatry of Covid-19, the BBB's secondary disturbances (Hernández-Fernández 2020) must result from initial still dubious direct immune-attacks and occasionally "Trojan" viral intrusions (Morgello 2020). SARS-2 (packed in vesicles) do invade some neurons (Gu 2005, Zubair 2020, Paniz-

Mondolfi 2020), rather than ECs of the plexus choroidei and ventricles, which otherwhise could provoke Idiopathic Intracranial Hypertension (IIH). Research, including such on CSF remains tenuous. SARS-2, measuring 100 nm (5-fold the size of "cracked" para-cellular pathways) requires vesicular trancytosis (Erickson 2021, Rapoport 2000). In vitro SARS-2 destabilizes the BBB: spike proteins cancel mRNA of tight junctions (TJs) and boost IL-6 or ACE2 on ECs (Reynolds & Mahajan 2021).

SARS-2 after docking onto membranous ACE2/Co-factor-points – beyond just injecting its RNA - *must* (not can) use clathrin- mediated (or putatively other) endocytosis (Bayati 2020, Petersen 2020, Yang & Shen 2020) which phenothiazines can block (Plaze 2020). SARS-2 attaches super-efficiently (Ellis 2021) through ACE2 which in differential brain regions is present on most also endothelial cells (H. Xu 2020), but occasionally too sparsely on MCs (Gebremeskel 2021) and other leukocytes to permit "Trojan" entries across the brain's barriers (Desforges 2019, Generoso 2021). Yet on MCs spike-RBD binding to ACE2 SARS-2 triggers degranulation and pneumonia (Wu 2021, Komaroff & Lipkin 2021). Covid-19 through multiple mimickries of human brain epitopes promotes auto-immunity (Gupta & Weaver 2021), again intensified by MCs (Brown & Hatfield 2012).

Much of the PNEI-literature pivots around the short-living «extremely unspecific» (Himmerich 2019) PICs. Yet about their access to the healthy cerebral parenchyma across the BBB - facilitated by "circulating factors" - "little is known" (Erickson & Banks 2018). An authoritative reference on «sickness behavior» cited five modes of access (Capuron & Miller 2011): 1.) pseudo-«humoral»: via choroid plexus and the circumventricular organ - only if concentrated (Walker 2013); 2.) saturable trans-endothelial: to-and-fro (Banks 1989, Erickson & Banks 2019); 3.) pseudo-transport: eliciting substituting luminal endothelial PICs (Watkins 1995); 4.) «neural» conveyance of PIC-signals: via vagal afferents (Maier 1998); 5.) pseudo-«cellular» carriage by monocytes sucked in after TNF-α. To this own proposals can be added of 6.) peripherically imprinted MCs entering the sane brain after intruding counter-current along abluminal arterial pathways (Treviranus 2017) deranged 7.) by the "nasal" pterygopalatine ganglion (PPG) damaged by SARS-2.

Also PICs-stimulated MCs - via the "RAGE/NF-κB"-pathway - release further PICs and recruit MCs while the BBB opens. RAGE - which also senses microbial alarming "patterns" granting them access – opens and inflames barriers through MMP-9. In humans (and mice) cerebral ACE2-receptors (but not TMPRSS) - very sparsely in the hippocampus, and *not* in the PFC- are found on neurons - and some companion cells. For the initial parenchymal access the EC's ACE2-expression is crucial and high in the choroid plexus - determining CSF-pressurization and potential viral spreading- or in the paraventricular thalamic nucleus - a hub for appropriative behavior, wakefulness, and stress-resilience controled by intruding MCs (Treviranus 2017, Fitzpatrick & Morrow 2017, Ren 2018). Meanwhile SARS-2-replication within, also sanctuary-resident, monocytes/Mφs – also in "Trojan horse" modes of cell-trafficking move centerfold (Yilla 2005, Nikitína 2020).

IMMUNOLOGICAL ANTI-SARS-COV-2-RESPONSES IN COVID-19

SARS-2 interacts with all adaptive immune cells, but T-cells seem to take the brunt with an often lethal dip (Zeng 2020). Again MCs orchestrate CD4+-T-cells by antigen-presentation (Li 2016). Within non-recovering lungs CD8+-T-cells maintain cytotoxicity via type-1-CKs and IL-17- with little resolving IL-10 from B-cells, who's antibody-excesses become deleterious. Covid-19 astonishes through widely perceived immuno-anomalies, maybe provoked by envelope-proteine E2, alone causing ARDS via attack pores (Xia et al. 2021). Anti-viral responses against SARS-2 are brought about atypically by PICs related to typ-2-interferon (INF) - but sparsely by type-1-INF needed against SARS-1, MERS or Influenza-A. While the asymptomatically infected show protection through active ribosomes, T-cells, B-cells or cell-killing, but low Th1-/Th17-cytokines, acute Covid-19 shows innate and adaptive-Th2-hyper-responses to INF-γ escalating into a "pro-inflammatory cytokine storm" (here PICKS), run up within white adipose tissue, ECs or pericytes – with running "deviated" *not* anti-viral (Méry 2020) Th17-cell responses. Research about PICKS traces "cytokine signatures" along cascades, long-non-coding RNAs or derailed antibody-productions, paralleling similar RNA-virus-diseases.

Mast cells as candidate relevant players at the brain's barriers

MCs are about to solve the conundrum, that the BBB in neuro-Covid-19 appears as disturbed without visible contributing cellular events. Although MCs have long been proven guardians at the "immune gate" to the brain (Theoharides 1990), they are neglected in relation to Covid-19 even by the pioneers.

Only the long-lived MCs are able of sequential "non-suicidary" etosis (MCET) - forceful expulsions of nuclear anti-microbial material provoking micro-macro-immuno-thromboses (Bonaventura 2021) - in proportion to stimulations by microbes (Komi & Kuebler 2021). This could generate focal transient intramural serial explosions, with rapid resolution as in MIS-C - or autism and atherosclerosis (Theoharides & Zhang 2011; Pertiwi 2021). Peri-intra-arterial MCET could well open sufficient leaks for SARS-2 to enter the parenchyma, the more as MCs are present along the 600 km of microvessels (Guimbal 2021) being abluminal residents of the arterial media – suffering from putative push-backs from failing arterio-intramural clearance and

possibly being restrained tonically via muscarinic PPG-efferents (Treviranus 2020) – unless suffering early attack by SARS-2 (Fagre 2020). MCs are hereby exposed to the wringing mechanisms of reverse intramural flow (CIMURAF, Treviranus 2019) and to their newly discovered domino-activation of TNF-α production through extracellular vesicles (Vukman 2020). MCs also cooperate closely with the "lymphatic cauldron" which opens in sepsis (Oliver 2020, Kunder 2009, 2011).

What the Dengue-virus teaches about Covid-19

Human MCs (without being invaded and unless blocked by stabilizers) after (granny-tyring) dengue-illness become "Th1-polarized" permeabilizing ECs the more their Fcγ-receptors absorb immune-complexes, which have been cleared by apheresis improving PASC, whereas dengue-infected MCs – besides performing antigen-presentation to unconventionally responding (γδ)T-cells (Mantri & St. John 2019) – the kind becoming decreased in severe Covid – make vessels leak through many mediators. MC-stabilization rebalances (immuno)-metabolism (Morrison 2017). Via MMP9-gelatinase MCs disrupt the ischemic BBB.

A prime role for mast cells and arteries in cerebral Covid-19?

Cerebral mast cells (CNS-MCs) besides residence-specific features lack IgE-, IgA-, and c-kit-receptors. Despite their unique faculties in entering the sane brain (Silvermann 2020, Silver & Curley 2013) – in contrast to Mφs (Lee 2021, Arcuri 2019) – MCs remain rarely discussed, and never as hypo-"activated". Yet all previously MC-"overactivated" patients from a first global mild-Covid-19-cohort noted a strikingly pervasive transient regression of their symptoms (Giannetti 2021). Similarly "urticarial" or autistic persons seem protected (Brondino 2021). The at times leaky low ACE2-density (J Li 2007) "lymphatic cauldron", MCs closely relate to, has received only marginal attention (Witte & Daley 2020).

Findings in severe Covid-19 point to a pivotal both protective and pathogenic (Rathore & St. John 2020) role of MCs (Tan 2021), which flavonoids might modulate (Theoharides 2020). MCs hereby, like in dengue-fever, parallel the overall response in being initially protective and then destructive by overactivation (Ricke 2021).

Interstitial clearance failure: SARS-CoV-2 attack the nasal ganglion

While anosmia with rarer ageusia is (not neuro-specifically) pathognomonic for early Covid-19, *all* PASC-cases present ORL-pathology (Davis 2021). The battles from the beginning take place inside noses and nasopharyngeal lymphoid tissues (Gallo 2020) since SARS-2 attacks the nasal mucosa early and even intraneurally (Meinhardt 2021). Among ganglia in deer mice (Fagre 2020) mainly the PPG and trigeminal one were SARS-2-antigen-positive (SAg2+) and attacked by neutrophils, as was the olfactory bulb; myeloid precursors were SAg2+ in the calvarial marrow – which is alimented through tubes from the meninges which allow MCs to determine calvarial bone and marrow in mice and men; (Cai 2019, Herisson 2020, Ogle 2004, Fong 2003, Dasgupta & Jeong 2019). Intranasally infected mice with humanized ACE2-receptors accordingly were SAg2+ in neurons, astrocytes, and microglia.

PASC/«LONG COVID-19»: SYNDROMATIC FATIGUE BEYOND BANALITY

Weakly correlated with in-hospital hypoxia Covid-19 in 42% months after still slowed cognition - half struggling with verbal recall. Besides cerebral derangements, feared among the elderly (Krupp 2021), the lasting or subsequently appearing (20%) PASC (see Table 3) is related to: the lungs, "cardiovascular" chest-tightness or MC-related cardiopathies (Dixit 2021, Kounis 2021).

Various pathomechanisms play: 1.) non-healing lesions or effects via intruded virus, persisting in sanctuaries/"reservoirs"; 2.) PICKS-derived also immunometabolic "scars" and ongoing slight (immuno-)thrombotic(-embolic) events and cytokine imbalances in blood, lymphatics (Witte & Daley 2020) or interstitium; 3.) IIH-like imbalances connected with CSF dynamics; 4.) endocrinopathies; 5.) secondarly advantaged noxious pathogens (Proal & VanElzakker 2021), including 6.) such subverting immune cells from inside (Treviranus 2020) or via dys-microbiosis (Rhoades 2021); 7.) coincidental or locally generated anti-cerebral autoimmunity; 8.) iatrogenic effects; 9.) subjective and objective psychosocial stresses, unhealthy life-styles and tertiary behaviors.

Vascular compliance explained: also against dysorthostasis in ME/CSF

Besides post-infectious «sickness syndromes» (Kealy 2020) after microbial challenges, the "myalgic encephalomyelitis/chronic fatigue syndrome(s)" (ME/CFS) in 0.4% of humans constitutes a, meddled (Twisk 2018), first reference when listening to patients who, after variously severe COVID-19-infections, stay or become crushed by fatigue (Komaroff & Lipkin 2021) after slightest physical (or mental) efforts - topped by obligatory post-exertional malaise (PEM). Persons with this unrewardingly health-care-consuming condition involving ECs lack recognition from social insurances despite highly resistant persisting fatigue and (in 86%) intolerance of orthostasis (IO) - often even when sitting (van Campen 2020). After an often infectious trigger ME/CFS`s day-long prodromes escalate into a bewildering array of (micro-macro)-abnormalities of moodiness, nausea, paraesthesia, or less often (head-)aches or rare gut problems (Ghali 2021) - pointing to a probable cephalic and not caudo-corporeal (possibly lymphatic) inflammatory source.

Table 3. Long COVID: Symptoms from international cohort over 7 months. Modified from: Davis HE (2021)

"LONG COVID-19" / PASC: SEVERITY & COURSE. Modif. After: Davis (2921) Long COVID: international cohort over 7 months:			
PASC	**Slight / Initial**	**Moderate** > 6 months: Recovering	**Very/Severe** (1:5) Moderate (2:3) Persistent
Nr. symptoms	11 (max. week 2)	17 (max. week 8)	14 > week 28
Main symptoms 100%: any ORL **>90% :** Fatigue Vegetative Respiration Musculoskeletal Sensorimotor **>80% :** Gut Cardiovascular **PEM -** Post-Exertional (physical , mental) Malaise Mood Cognition **>70% :** Sleep Headache Memory **45 - < 70%:** Reproduction / Hormones Skin, Smell & Taste **15 - 25%:** Attention Hair-loss Dyspnea Hallucinatory Auto-/Immune symptoms		**Worst problems** **Fatigue** 78% ↘45% **PEM** (mental & physical) > 70% Breathing Cognitive 55%	**Worst problems** 86% ↗ under stress Fatigue 87% Job: less 45% Job: none 22%. **PEM** (mental & physical) 72% Breathing Cognitive <u>Antibodies</u>: Celiac, RA, rare ANA,
Cl.1: improving Diarrhea/Vomit. Slight ORL Fever	Cl.2-A: improving Nausea Smell & Taste POTS-like faints Respiration & ORL Aches / Chest	Cl.2-B: stable **Fatigue**, Head-Aches, Bones Sudden dizziness Sleep / Halluc. /Slurr. Covid-toe	Cl.3: deteriorating Brain fog Bladder Menstrual **PEM** Joints Neuralgia Motricity Memory Eye Hearing Tinnitus Reflux Constipation Speech Language Inflamed veins Rashes Derm.graphia **NEW** allergies
	Lymphatics?	MC: Kounis-syndrome MC: Takotsubo	Anti-Phospholipid Ab Anti-IFN- Antibodies
MCTC skin brain "connective" (lung) submucosal gut Tryptase (Chymase) Meningo-arterio-parenchymal MCs Nasal lamina prop.	Lung: ↘ IL-4 IL-13 C3a C5a complement-receptor MRGPRX2-receptor Long-living		**NEW** anaphylaxia IgE? Pseudo-Anaphylaxia ? **MRGPRX2-receptor** [Kumar 2021] (also Basophils)
MCT "mucosa" Lung alveola, gastric Tryptase-only Many brain MCs Nasal epithel	Lung: ↘ IL-5 IL-6 Not long-living		**NEW** anaphylaxia IgE? Vaccine anaphylaxia ? [0.03%]
Mast cells mature inside tissues where they exert a "rheostatic" function according to a not simply "connective" to "mucosal" spectrum. (Frossi 2017; Gurish & Austin 2012). After lung-Covid-19 conjoined celiac TG- or RA-related antibodies could be risk (Lingel 2021)			

Normal orthostasis induces immediate autoregulation of cerebrovascular vessel changing diameter (resistance) but also "compliance" by, quicker, distensibility (Brassard 2021) remaining moderately preserved in OI. Distensibility with constant diameter – also in the brain – remains mysterious without considering the hidden pervasive aortic blueprint of arteries and the resulting "Cerebral IntraMUral Reverse Arterial Flow" (CIMURAF-model; Treviranus 2018, 2019, 2020) constantly pushing axially wrung coronal compartments bounded by "candy-cracker" twists (…) at the borders to relaxation (…) towards the extracranial arterio-lymphatic outlet. These chambers - moving under plausible peristaltic control from the checker-board-like PPG efferents by its stimulations – conceivingly can be narrowed (pressurized) or distended (depressuriezed) following the narrowing or broadening of coronal zones of (radial, but mostly alternatingly sensed circumferential) muscular contractions - solving for the first time the riddle of "softness without distention" of more non-individual (Zamir 2007) "apparent vascular compliance" responding with impedances to pulsatile flow (Hu 2006, Moir 2020). The peristaltic steering in fact may well anticipate pulsatile peaks by some feed-forward reflex or axial ionic signaling. CIMURAF also explains (b.) the lower coronal than axial resistance explaining recent OI-findings (Finkelmeyer 2018): (c.) long-term parenchymal stiffening through interstitial clearance failure causing "interstitial fluidopathy" (Taoka & Naganawa 2021) and (d.) increases in CBF cooling consequential overheating – also resulting in an added radial pressurization of the arterial wall, conceivingly hampering CIMURAF (transversing the media).

CIMURAF being plausibly steered by the PPG (Treviranus 2020) – given its efferents` architecture and neurochemistry (Nizari 2021) – this implies a putative prime pathogenic role for PPG in Covid-19, since SARS-2 inflames and colonizes it. Considering that if CIMURAF is (mis-)directed by the invaded PPG in Covid-19, its disturbances – troubling a newly postulated role as vascular and/or interstitial compliance modulator – plausibly result both in fatigue-inducing brain inflammation after dysfunctions of the BBB (also by MCs unleashed by the PPG), and their strain by autoregulatory failures.

Idiopathic Intracranial Hypertension: choroid plexus, leptin, mast cells

Headache and fatigue defining IIH are also frequent in ME/CFS as are cognitive troubles, low mood, dizziness, and aches. While the normal-sized choroid plexus in IIH harbor a treatable hypersecretion causing a quicker aquaeductal flow generating higher pulsatile peaks, they are surrounded by barrier-opening MCs (Zhuang 1996). IIH lessens with lowering of obese body weight, itself proportional to increased leptin, which is increased in IIH maybe by boosting choroideal ion transport (Alimajstorovic 2020). In COVID-19 such adipokines decide on survival and leptin by immuno-metabolism also shifts MCs and Mφs towards vasculo-inflammatory modes (Żelechowska 2018) explaining the doubled cardio-vascular risk in IIH and possibly its tiring symptomatology because MC may permeabilize the choroid plexus (Turygi 2005).

MC and the PPG in Covid-19 (and ME/CSF)

The extrinsic innervation to neurovascular units (NVU) fades out with the Virchow-Robin spaces (VRS). Its parasympathetic part stems mostly from the PPG, which is therapeutically stimulated to transiently open the BBB (Schmidt 2019). Only its cholinergic output to the cerebrovascular arteries, before approaching Willi's circle, from the internal ethmoïd arteries in front, passes through a rete over the cribriforme plate (Norwood 2019, Hsu 2019), the ethmoïd roof perforated by olfactory nerves being again accompanied by channels draining CSF (and cells) into the nasal lymphatics (Carare 2014, Hara & Weir 1986, Suzuki 1990b). This cribriforme plate lies in SARS-2` initial attack zone. Inhibition of PPG's efferent periarterial functions (e. g. CIMURAF, MC-inhibition) by the trigeminally-relayed Suzuki-afferents could explain why gingivitis (also by IL-27) increases Covid-19`s severity 3.5-fold (Marouf 2021).

Although CIMURAF through the hidden "aortic blueprint" of all arteries first interpreted the cerebral intramural clearance by muscular force (Treviranus 2018, Aldea 2019) the analogous mechanisms for extracranial arteries has not been explicitly postulated. Similar neutrally driven torsional coronal chambers can be supposed to heavily influence the behavior of abluminal and adventitial MCs – also in the context of the core COVID-19 (micro-)thrombotic events.

MICROBIAL NICHES, BCG, AND THE ANCIENT SARS-2 – ORO-MYCOBACTERIAL OVERLAP

SARS-2 enters microbial niches (Proal & Van Elzakker 2021) – possibly even by reactivating "free-loaders" or by hijacking already subverted myeloid cells e. g. by ingenious mycobacteria (Treviranus 2019). In latent or acute TBC – the normal daily killer at pandemic's levels – low whole-blood-plasma INF-γ responses to SARS-2-spike-protein by shared gene expression revealed overlapping hypo-immunity (Petrone 2021) among circulating myeloid subpopulations: IFN-γ and TNF-α were increased in both active TBC and Covid-19 and lacking in latent TBC or Influenza (Sheerin 2020). If this should extend to parts of the "oral mycobiome" it might explain the gingival SARS-2-sanctuary and periodontitis is a risk factor for infection and severe Covid-19.

Crude epidemiology corroborates the miracle BCG as a means to revert the Warburg-effect - providing ready-made intermediary products for rapid synthesis (at high cost) - interacting with Covid-19 mortality.

BCG-proteomics revealed MCH-I-restricted epitopes made of short very primordial conserved sequences overlapping exceptionally between SARS-2-epitopes which *both* T-cells and B-cells target (Urbán 2020).

CONCLUSIONS AND OUTLOOK

The PASC resembling unresolving SARS-cases at the moment of writing looms as an undecided prediction. Unexplored remains the role of neural or direct openings of the "lymphatic cauldron". Such unresolving – often microbial – challenges presenting with a huge variety of responses - beyond the pervasive roles for mast cells (as also sequentially "etosis-practicing" trespassers across sane brain barriers) appear also to be rooted in the here proposed new pathophysiological models for a.) orthostatically focussed chronic fatigue and b.) intracranial hypertension. Covid-19 by starting at the nasal entry with a 1st-attack on the social-stress- and facially-sensitive nasal ganglion mis-directs the cerebral arterial intramural clearance normally offering pulse-anticipating minute "compliance" by varying the width of wrung sliding chambers. Mental health rehabilitation starts with advocating a new soft-neurological-psychiatric liaison. Wether BCG or furutre vaccines training the innate system (e.g. against anxio-depression) will help in this remains to be seen.

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