TETRAD Institute of Complex System Dynamics

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Preliminary observations pertaining to investigation of underlying chronic stressor agents in principally autonomic signaling that integrate immune response to inflammatory conditions and outbreaks

Key points:

- **These consequences may often include responses to infectious foreign-agent diseases and psychological duress without indicators of external infection.**
- **The outcomes may often lead to conventional inflammatory response, overreaction, autoimmune disease, dysautonomia and arrhythmia.**
- **There may be specific genetic configurations that indicate sensitivity and disposition to stronger reactions, and some of these may lead into major observed disorders and diseases such as MS, ALS, Parkinson's, Alzheimer's, POTS, ME/CFS, and other conditions.**

M J Dudziak

Table of Contents

This memo addresses things that pertain to the Neuroplex-C project and other aspects of TBD, TND, PSD research which involve TETRAD Institute and several collaborators in academic, medical, and corporate centers of research and clinical practices. At the close of this memo are URLs to supplementary materials that are presently available for access.

§ 1 Preliminary Remarks

Background and Foundations
These notes do not stand alone but go with other materials, especially the work of many others.

[1] See some of the background and bibliographic materials @ http://neuroplex-c.tdyn.org. More will be added in coming updates (including work by: Arnold, Chung, Blitshteyn, Boris, Brizhnik, Eccles, Fang, Fedorowski, Frelick, Gilvad, Granichin, Johanssen, Lee, Luther, Magnusson, Mathias, Maucher, Parlitz, Seo, Song, Stahlberg, Stiles, Sutcliffe, Tomasson, Tomson, Treisman – some references here but most in the other papers and bibliographies).

[2] What is here builds upon a few specific pre-publication/limited-circulation sets of notes that include some not openly listed at the above website (of which there are several documents – see the menu for that site) or at other sites. These include:

> http://neuroplex-c.tdyn.org/not-open-public/npc-pasc-inflamm-autoimmune_extended-abstr-summary_mjd_18dec21.pdf
> (The predecessor to this set of notes, and some similar content, but more on the Population Health Equity bioinformatics resources)
>
> http://neuroplex-c.tdyn.org/not-open-public/pandemic-disease-progressions-and-future-expectations_v1_mjd_08dec21.pdf
> (More specific on COVID-19 and PASC - "Long COVID")
>
> http://neuroplex-c.tdyn.org/not-open-public/tbd-ances-framework-synopsis_mjd_v1-0_28oct21_0315.pdf
> (The longer piece that goes into a lot of the foundational substance including theoretical models and connections with physics and biophysics)

Motivation
The present document is intended as a stepping-stone, a "diving board", for constructive discussion, particularly among recipients! What is here constitutes "integrative" as well as "new perspective" thinking. But we need to compile the data from what has already been done, by many, and then begin looking at things in a "new light" - and then, with reference to what has been presented in other documents, notably the "framework synopsis" piece listed above), a new set of experiments and simulations, modeling, to refine the mathematics and connect with the observed clinical findings.

Roots
The roots of what is being shaped here spread out in several directions and not only with work of MJD and others affiliated in and with TETRAD Institute. The foundations rest strongly on work done, presented, disseminated, and ongoing with several others (see the list of names above); the list is long and should be – will be – in any formal publications (of which this is not) or formal proposals, presentations, etc.

The broader public population health equity picture

All of this work, this entire line of reasoning, and the fundamental concept of "Complex Medicine" (see further below), is very, very centrally linked with what many in the health science fields are recognizing, in recent years, and especially since COVID-19 came upon our world, as a need to rethink and reshape how we do Public Health. Not only for epidemiology, but across-the-board.

Population health inequalities and the need for creating equitable, balanced health systems comes first in changing our thinking about these population and their differences and their inter-connections and inter-dependencies, and realizing the Fact that only when we are giving more equitable attention, across the board, to all the variants in the population, will we be able to achieve better healthcare outcomes - for individuals, for societies (and also, for the economies of those societies, which occupy so much attention first and foremost with so many people).[1]

Some of this pertains to the ongoing work with the Population Health Equity Bioinformatics Resource (PHEBR) – a data bank for acquiring and deriving, including by inference, many patient characteristics and behaviors pertaining to a wide class of disorders and diseases that are being "integrated" within an evolving theoretical and experimentally-verifiable model.

What we are going into here, with hypotheses, observations, claims and arguments for doing further research together and collaboratively, is such that it necessarily, clearly, requires both:

- more population data than almost all researchers in some of the specialized areas have ever had access to, or that has ever been assembled, with such wholistic and systemic viewpoints as we express here
- more cross-disciplinary thinking and more willingness to work with people who are not "the same" in certain academic and clinical backgrounds and orientations.

What is not in this document

These are notes. There are not, here, the usual tonnes of references to many publications and other findings. They exist, and there is no paucity of data. Some, most of the authors mentioned here, have presented a wealth of information including experimental results. The point here is to begin to develop a top-down approach for integrating such results from many sources that show connectivity and support for a new understanding that can address why there are so many different forms of:

- inflammation, and not only in the context of infectious foreign microorganisms
- degradation and attack by "self" mechanisms that are generally considered to be protective against external threats
- common elements of dysfunction that involve interference within wave mechanics, in neural and fluidic pathways
- significances of a group of tissue types that heretofore have often, in medicine, been ignored or relegated to being somewhat less "significant" and not as "critical" as the major attention

1 Simply put, just as with the healthcare for any one individual, so the same for the Society – the "social body". One cannot ignore various "parts" of the Body, and only give attention and care to one "part" or a few "parts", to the exclusion and ignore-ing of the rest. This is not only in the case of the obvious epidemiological processes of transmissible infections like certain viral/bacterial diseases. This is just as much about cardiovascular, pulmonary, gastrointestinal, and psychiatric disorders. All the "parts" will have better health outcomes when all the "parts" are being attended-to - equitably, fairly, rationally.

> subsystems of organs and networks such as cardiovascular and neural – namely, connective tissues, skin layers, ligaments, tendons, muscles, bones. We begin to think here that these tissues have historically been overlooked in medicine and that we may be missing things of importance with regard to not only diagnosis and therapy but for understanding the etiology of many of the diseases of special interest here.

Goals for Collaboration and Teaming

This entire approach, this multi-faceted, multi-phase project, including the clear and near-term public health values it brings, also requires that we find ways to address the basic fact that some research does require modest but definite funding and receptive, affirmative, forward-moving support from persons who are in positions of prior and current recognition, institutional authority, and bureaucratic game-mastering.

One of the key requirements for bridging many of the gaps faced, up to now, in many inter-disciplinary areas of research and clinical studies, is to be able to bring together and co-manage teams of specialists and experts who are in widely separated institutions, geographically, worldwide. The facts of the COVID and post-COVID (lingering COVID) global experience, advancing and in some cases forcing and enforcing the use of teleconferencing, remote work, distance-based employment, teaching, and collaboration – all of this has, above and beyond the social and personal difficulties imposed upon so many of us, brought about a greater acceptance and ease in doing things as teams, as partners, as true collaborators, even though many of us are separated physically. Nonetheless, some tasks require being "face to face" and "in person". Fortunately, for some of us, these possibilities exist and are relatively doable, feasible, practical – so long as there are mechanisms to make such meetings and in-person collaborations possible.

§ 2 Introduction

Research and clinical studies, globally, provide the rock-solid basis for the assertion that what are termed *neuroelectrochemical stressors* – within the range of sources indicated above, namely,

> actual physical "3d" entities that are chemical and biological, but also physical acoustic and electromagnetic signals, and very importantly, also psychological stressors which are all a complex, obviously, of external-origin and internal-generation sources (the latter being within the brain, yes, but also in other visceral reaction processes) –

are a major contributing factor – even beyond genetic factors, albeit involving genetics, absolutely – that lead into subsequent disorders and diseases of the types indicated by the following very general list (see further below). Understand here that we are not suggesting or claiming at all a singular common causal mechanism, but an underlying functional pathway of

stressor → defensive-type systemic reactions → pathologies

that break down functions within those systems reacting in essentially self-preservation, self-sustenance, self-preservation.

Pathologies of special interest and relevance

The general list of our consideration at this point in our work spans a very wide range of observed pathologies (all of which are addressed in greater detail further below or else considered as "what we need to work on together!"):

- Inflammation and inflammatory-type reactions which include "psychological inflammation" (thus, meaning, inflammation as we know it, medically, from **infectious foreign-agent diseases and also from psychological duress without indicators of external infection)**

- **Certain (at least) autoimmune disorders and diseases**

- **Fundamental dysautonomia, where we see dysfunction in the communications within and by the sympathetic and parasympathetic networks and the end-effector tissues and organs with which they connect**

- **Cardiovascular, pulmonary, gastrointestinal and potentially other systemic arrhythmia in both the "classic" interpretation (e.g., cardiac types) and other behaviors that are phenomenologically similar but not generally classified as such (e.g., IBS).**

- **Disorders and diseases that historically are labeled "syndromes" and often "bundled" into categories of POTS, ME/CFS, MALS, hypermobility, EDS.**

- **Specific major autoimmune-related and autoimmune-implicated diseases such as MS, ALS, Parkinson's, Alzheimer's, Lupus.**

Figures 1-4 on the following page provides a first-cut illustration of the overall logic and the resulting model which we believe has merit in aiding to integrate many seemingly disparate "parts" of the challenge in medicine today with respect to understanding the common ground and interdependencies among these different diseases and syndromes.

Note that in the Appendix can be found earlier figures that also help to explain the basic theoretical and biomedical model.

Figure 5 provides a first-cut map of the overall diagnostic and therapeutic model which we believe can be built through a collaborative approach that takes into account the theoretical model and what we expect will be discovered, corrected and improved by having more open and fluid communications with dedicated experts in the specific areas that matter.

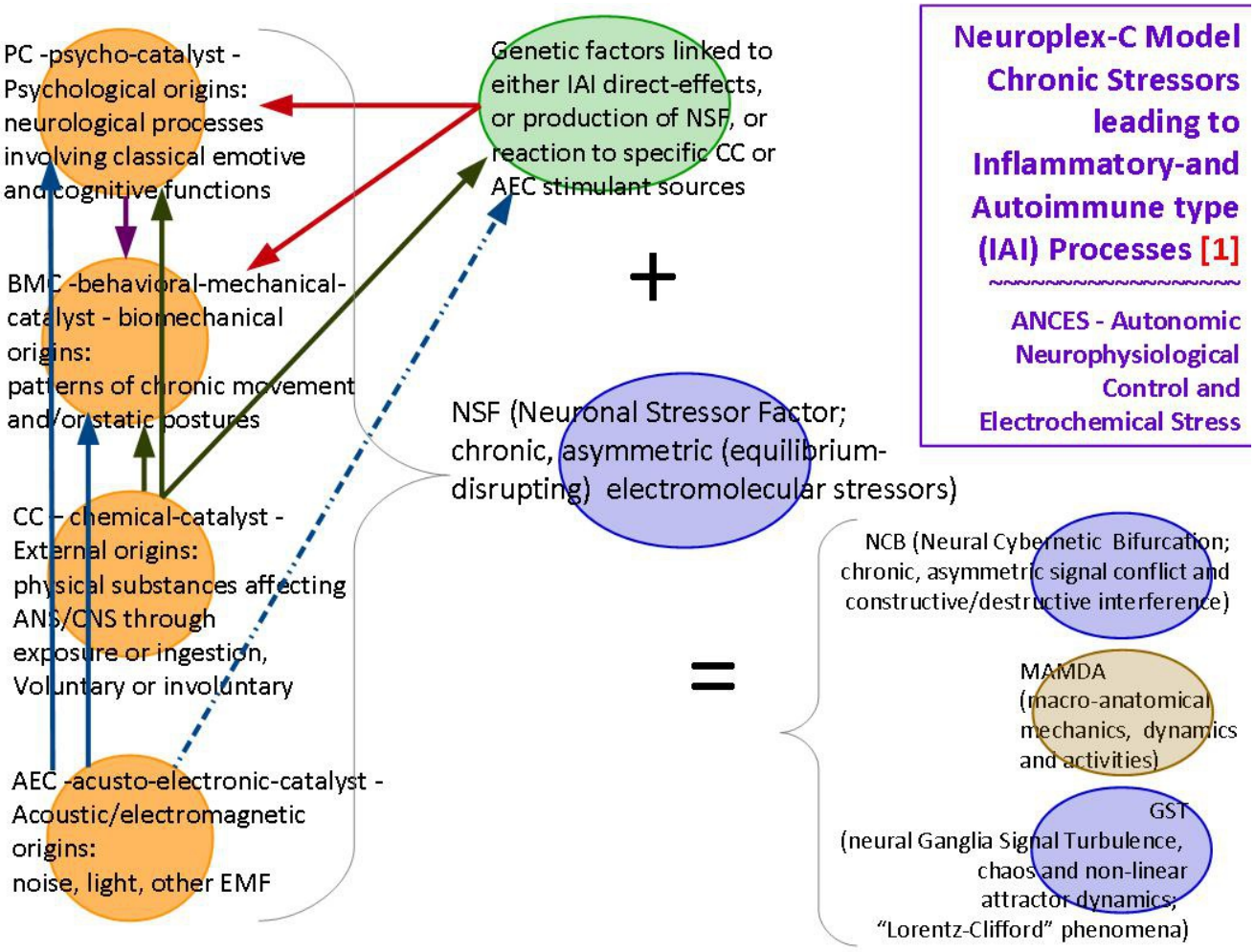


Figure 1 – the basic NPC (Neuroplex-C) model (1 of 4)

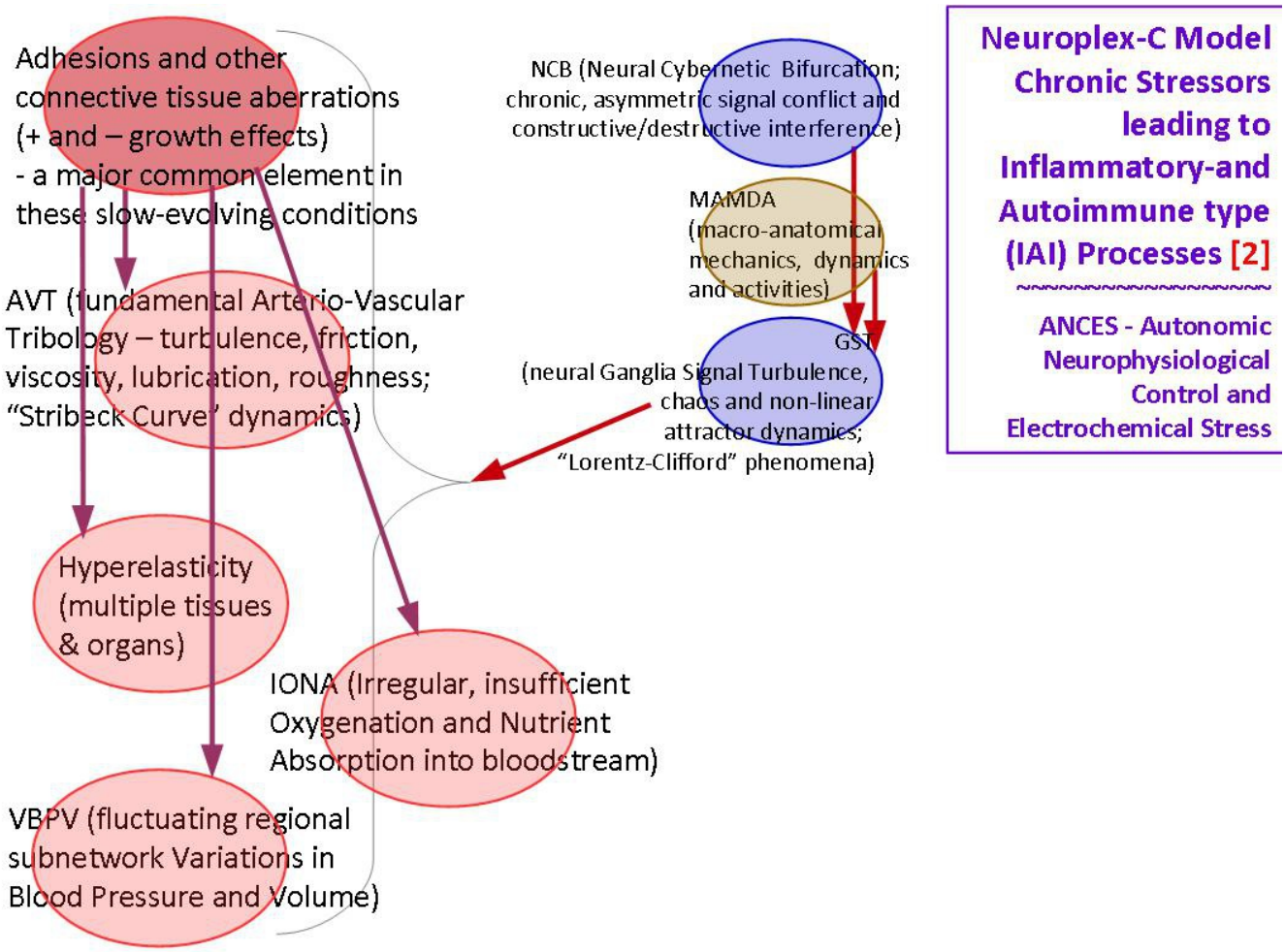


Figure 2 – the basic NPC (Neuroplex-C) model (2 of 4)

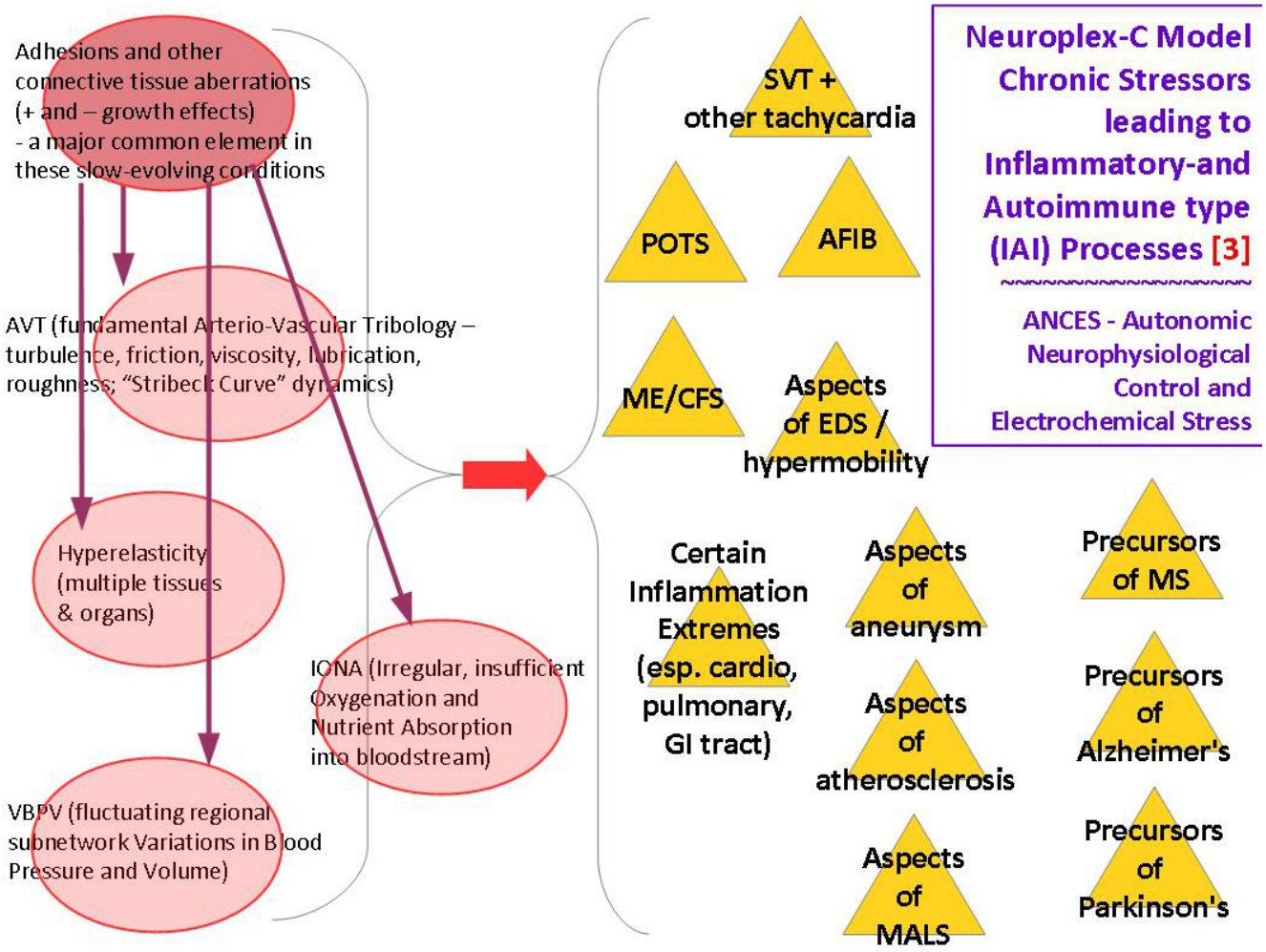


Figure 3 – the basic NPC (Neuroplex-C) model (3 of 4)

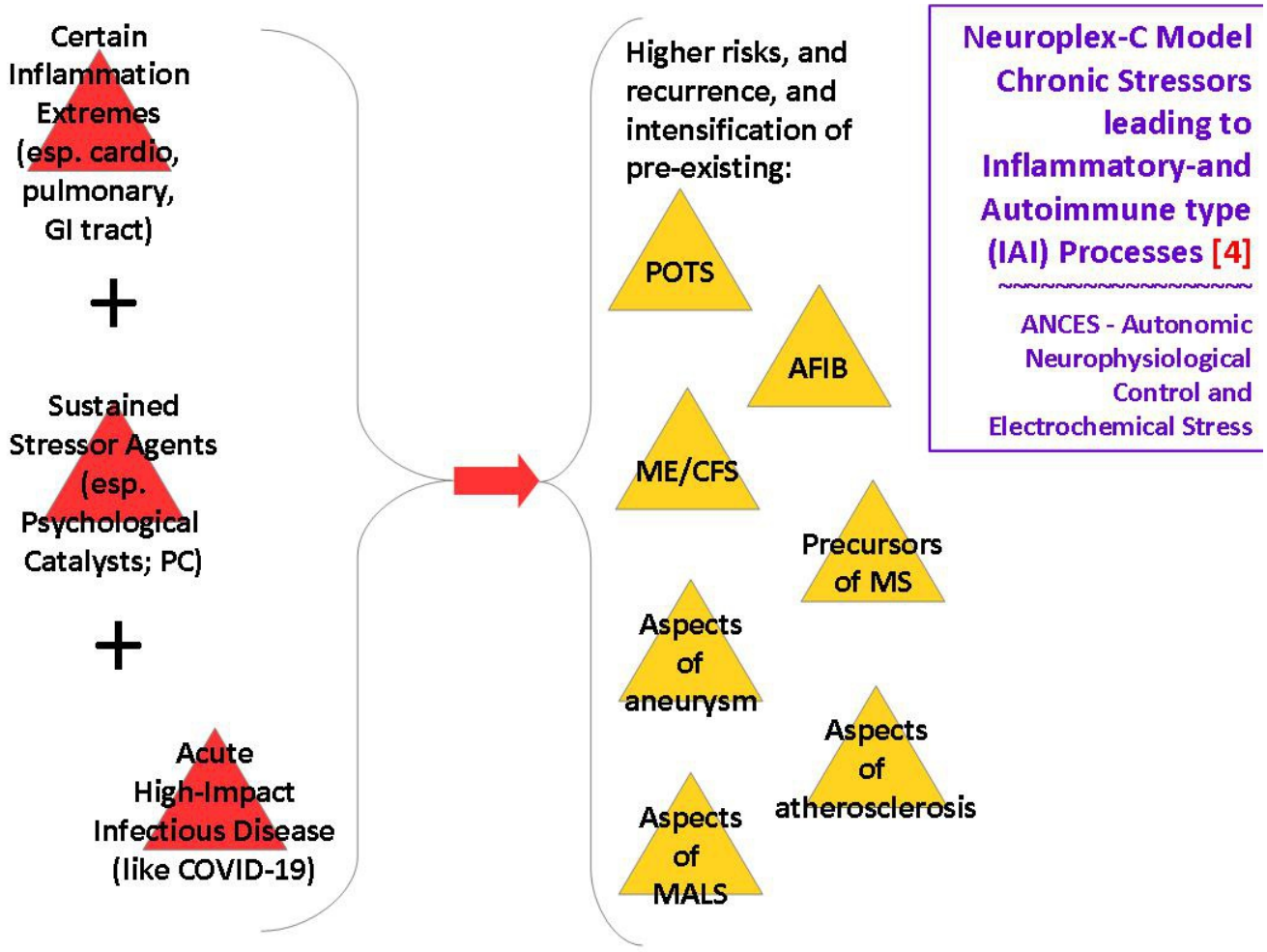


Figure 4 – the basic NPC (Neuroplex-C) model (4 of 4)

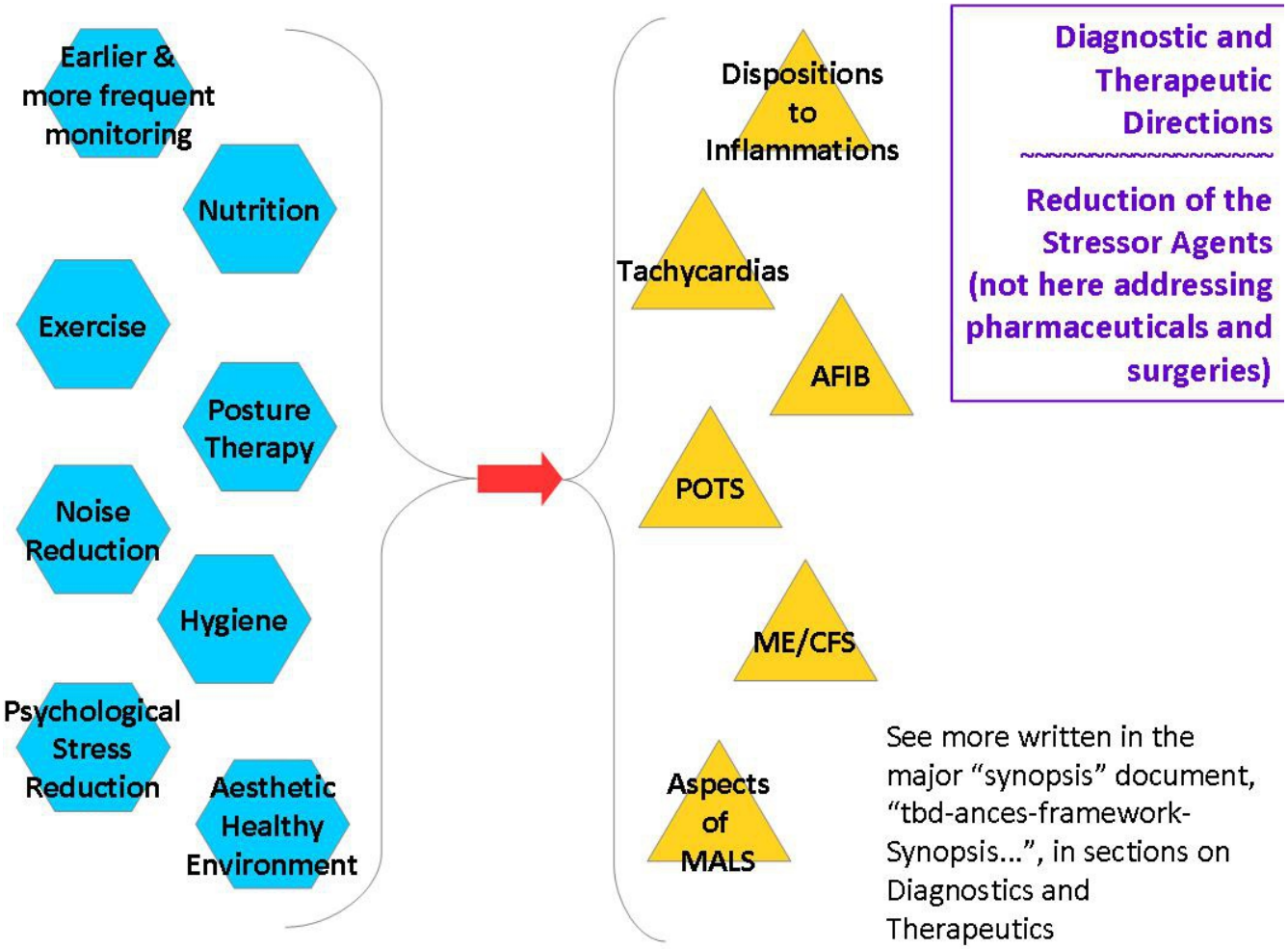


Figure 5 – the diagnostic and therapeutic approaches possible

Genetics – introductory comments to "reset the stage of our microscopes"[2]
We note here, early on, that there may be (and all indications are) specific genetic configurations that indicate sensitivity and disposition to the metabolic activity that is involved in such major observed disorders and diseases such as, and other conditions. However, our perspective is, in general, a bit different than what seems to be the dominant trend in thinking.

Perhaps some simple restatement early-on can help. This will be explicated further, as we go on (and not necessarily all at once in these notes!).

Genes provides the instruction sets, the codes, for making and not making, for assembly functions (+ or -), for a range of polypeptides. Nobody will dispute this. However, the old-era, Turing-type and rather simplistic model of genetics as being the "computer" of cells and living systems, this is mostly gone in contemporary research, thankfully, but it lingers and influences.

So, we consider:
Genes may be implicated in many pathologies by either activation or deactivation, one of the two functional outcomes (they will be either "on" or "off"), because of whatever they cause as such a consequence, outside the nucleus, to be performed in the next-logical-layer of cellular "computation". That "algorithmic" action is what those proteins DO within the cell, their Work. It is how they influence signaling, communication, that takes place between the cell and its environment, including of course, other cells, and so on. The "parallel processing network", the "communication dynamic sequential and parallel processing" that constitutes the Life of the organism.

Genetic activation and deactivation pathways and trigger-functions therein
But what we do not know well, at least not yet, evidently, is enough concerning the pathways – and this can be best to think first of these as logical pathways, and then to examine the biochemical mechanics involved – which are involved in how certain specific genes are activated or deactivated, by agents – chemical in form, sure, but deriving from what we will temporarily call "aggravating, chronic, stressor-agents and stress-concentrated environments". These are, getting back to our earlier remarks in this Introduction, those:

- **interference patterns, both constructive and destructive, within actual neural signaling**
- **aggravations of neuronal axon sheaths and internal microtubules, creating conditions that lend themselves, or simply bring about, other specific degradation (e.g., amyloid actions) that form the "substrate" of degradation diseases (e.g., MD, Alzheimer's in particular).**
- **noise, turbulence, and flux of non-linear dynamical behaviors involving a great many moments and instances of bifurcation points, instabilities, non-linear attractor cycles[3] and**

2 The metaphor here is that we are looking inwardly, and not, of course, only with microscopes as such, but observing from the macro to the micro, and that we need to adjust and "reset" things with our methods of observation, our orientations, our perspectives, including the "rules" by which we accept, classify, and conclude causal and synchronistic relationships

3 e.g., Lorentz and Clifford types of what are in the vernacular termed "strange attractors" - not true chaotic functions which are actually deterministic through PDE (partial differential equation) analytics

catastrophe function topologies

- **effects of the latter, as complex neurochemical behaviors within the CNS, particularly within the cognitive and emotive regions of the brain, leading to a positive feedback loop involving all of these classes of stress agents and environmental conditions**

- **systemic chaotic behavior, including specific arrhythmias, that are then the more "explicit" (as well as more obvious) causal factors in pathological developments such as myocarditis, atherosclerotic and thrombotic activities, and other higher-order, higher-scale, larger-scope (in terms of tissues and regions) dysfunction within the organ systems involved.**

"Positive feedback loop" (PF Loop) is in our view the critical overall process involved in much of what we are examining and discussing. Such dynamics are, generally, inherently, bad for any system, particularly living ones. We consider that PF Loops lead to processes where the overall system attempts, in efforts for self-preservation, re-balancing, staying alive and doing as best as possible to "make-do" under adverse circumstances, will engage in what we then observe and classify as "inflammation" and as "autoimmune" disorder/disease.

We are aiming to find common grounds, common roots, beginning in abstract, logical, and computation-like models of biology and physiology, in order that we may discover common algorithms, common biophysical, biochemical and biomechanical processes, that we can then address with corrective measures, for that re-balancing, for effectively changing the PF Loops so that they will reset and so that the living system – the Person, to get direct and personal here – can return to a normal life without the body struggling desperately with autoimmune type reactions.

<u>Pathologies as they occur</u>

Now we consider some of the medical aspects. Many of the pathologies mentioned above occur at different times in the life cycles of people and not in specific conditions. However, many, particularly those we see associated with "chronic" and "autoimmune" attached as labels, do appear to share some things in common. We need to be asking more, and more openly and clearly, "Why?"

These pathologies commence particularly in adolescence and middle age and the outcomes are almost universally of only two types:

- extraordinary complications, disabilities and comorbidities, reducing the potentials for a normal lifestyle (including employment and a professional life) and for an average-length lifespan
- early and often sudden death – if untreated, and particularly, if unaddressed early-on

Most significantly, in terms of what can lead to a new understanding of the relations between several "syndromic" disorders and diseases, we notice now, 2020+, due to the COVID-19 pandemic, that both can be linked with viral infections (such as COVID-19,m but not only). This is part of how the whole "base" (basis) of the Neuroplex-C Project has originated and evolved. Autonomic nervous system function and dysfunction, and in cardiomyopathic pathologies, including arrhythmias, and in the connections emerging with inflammation in general and certain autoimmune diseases in particular – these are even more "connected together" and in causal processes, given what we are seeing, in very large numbers, through the COVID pandemic. Now, we are seeing increasingly:

- associations between COVID-19 (and its "long" form, PASC, and potentially other viral infectious diseases) with cardiomyopathy, POTS, MALS, hypermobility

- associations between the same and several classically-termed psychological and psychiatric disorders, notably depression and PTSD. [14] [16] [17]

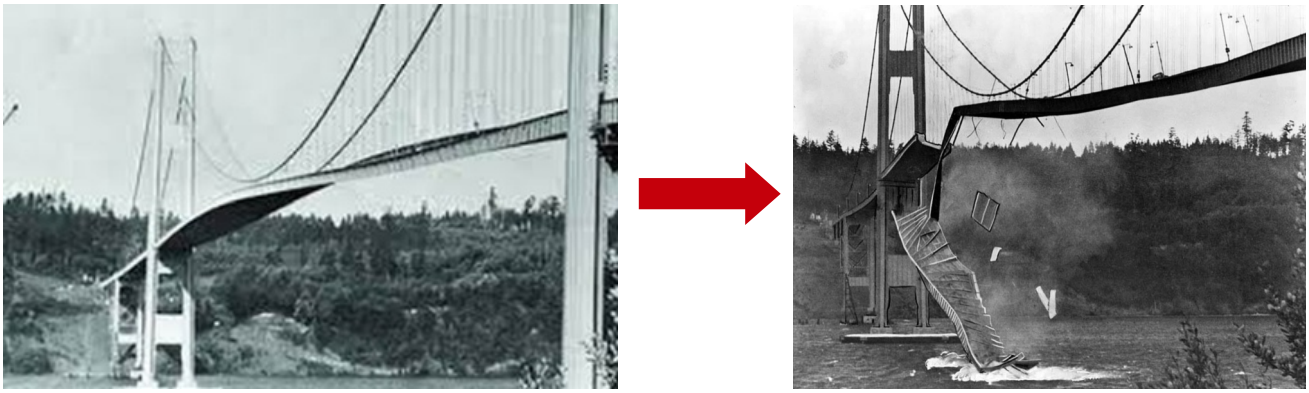
Keywords for all of this
The keyword-list for the remarks here are similar to those from an earlier set of notes:
Arrhythmia, Autoimmune, COVID-19, Dysautonomia, Inflammation, IBS, PASC ("Long COVID"), POTS with specific attention to ACE, ACE2, Ang (1-7), Ang II, ARB.

But we will add also here a few more:
bifurcation, turbulence, chaos, noise, positive feedback, ME, CFS, connective tissue disorders, hyper-and hypo- mobility, aggravated stress, PTSD, and a much-used, too-broad, and often-ignored term, because it contributes so heavily to much of this, abuse

With respect to the last term, "abuse", we mean here, a whole spectrum of forms, many of which do not involve the explicit and obvious physical forms. Bad words, bad tones, bad sounds. Too much, too long, it has the same effect on the psychophysical organism called "human being" as when there is constant hammering and beating on a stone or on a beam of wood or steel, or when the wind shears go every which way and build up constructive interference (in terms of amplitudes and the wave energy) but very negative and destructive in outcomes for whatever depends upon not having such interferences.

Sometimes, simple physics, simple mechanics (and also, for later consideration, the physics of tribology, by the way) can give us indicators of what is going on in the complex world of biology.

A few pictures can tell thousands of words



A strong claim that will irritate some but hopefully not all

When we will recognize and deal with the facts that the sounds and sights that fill our lives in our homes, workplaces, commuting, and daily lives in all respects, but especially in the places that are instinctively "supposed to be" and "expected to be" the Safe Places, are having a dramatic and destructive input to chronic stressors in people's lives – from childhood, even from infancy – then we can begin to have a better handle on how

- many major disorders of the types listed here
- begin to show up by adolescence, and if not, then often in early adulthood
- get worse either gradually or sometimes rapidly, depending upon circumstances, the individual's "constitution" and "condition", and those genetic factors which react or do not so much
- are often chronic, un-"curable", allowing for only, at best, palliative and "adjustment" treatment (including actual or virtual dependence upon pharmaceuticals), and
- are often terminal or giving rise to permanent comorbidities

§ 3 ANCES and Whole Body (including Connective Tissue, Bone, Muscle, Skin)

The ANCES theoretical framework provides one particular avenue of promise for providing a deeper understanding of the etiology and metabolism of several conditions and disorders that are often relegated to the category of "syndrome" and also not viewed as having pathologically supportive relationships among each other. While this research direction is by no means the primary near-term motivation for PHEBR, given other conditions and diseases as previously indicated, the value for exploratory investigations is high considering the potential beneficial outcomes for both theory and clinical practice.

The following key points summarize Autonomic Neurophysiological Control and Electromolecular Stress (ANCES) (and the role of chronic exposure to and metabolism involving a large class of neuro-electrochemical stressors) and provide a view into new research that can bear substantial benefits for a very large segment of the human population.

♢ Ganglial turbulence and noise (basal ganglia and peripheral nervous system (PNS) ganglia)
♢ Signal conflict and neuronal constructive/destructive interference wave patterns
♢ Growth-formation of ganglia tangles and knots
→ → → ♢ observed dysautonomic and arrhythmic reactions
→ → → ♢ repetitive and episodic disorders leading into chronic pathologically stable disease
→ → → ♢ inflammatory response as a chronic condition leading to autoimmune reactions and reduction in immune system strength for resistance to external pathogens (and other general inflammatory consequences)

3.1

Summary of possible consequences of chronic traumatizing turbulence within the CNS and ANS that may be attributed to neuro-electrochemical stressor agents

[typical trigger period]	[conditions]
[early infancy, < 1 year]	SIDS
[adolescence/young adult]	MS, Lupus, CFS, cardiac arrhythmia, POTS
[middle/later adult]	sexual dysfunctions, IBS, Crone's, other cardiac arrhythmia
[older adult]	(triggering/exacerbating) Alzheimer's, Parkinson's, AFIB, atherosclerosis

3.2

Epidermis, dermis, subcutaneous, adipose and epidural tissues, bone, muscle, tendon, ligament, and connective tissues.

There is a tendency, certainly among the general population, in the cultural "vernacular", to regard most of these tissues, and certainly those that are generally labeled as "connective" or "supportive", as being somehow "less important" than what we generally pay greater attention to. Brain, heart, lungs, GI tract, all the organs and glands. This is understandable. Often, it is within those organ systems that we find the most serious forms and consequences, often lethal, for diseases that go unattended and untreated. Often, with obvious exceptions from cancer and infections, the first group is not usually seen – not usually felt or regarded – both by patient and physician – as the main source of some problem, particularly of the sort that can lead in a relatively short order of time to severe illness, disability and/or death.

Consider the viewpoint that emphasizes in the abstract, the singular Whole Person. A perspective wherein the organs and their networks of action (e.g., arteries and veins, nerves, lymphatic network) are the specialized support entities for that Whole Person (no argument there) and where they perform their specialized functions not only through the obvious and customary "networks"(blood vessels, ducts, nerves, gastrointestinal, urinary and reproductive channels), but where – less obvious, less "in one's face", less prominent, but incredibly functional and essential – are the interactions with and through those connective-supportive tissues.

What we are getting at, suggesting here, is that a deeper understanding of the dysautonomic, arrhythmic, convulsive, chaotic, and through that, inflammatory and autoimmune-destructive, pathologies that we are here bringing together into an abstract "common space of cause and function", can emerge when we view these connective-supportive tissues in a "different light".

This "different light" is about those tissues' active role in forming, shaping, and controlling those behaviors that we see, both normal and pathological, within those organ systems.

Consider here in bullet-point form, briefly, and please expect and assume that yes, there are a lot of prior research and clinical studies, by many many others, that supports how this view has arisen and why it is even occurring, here, and why we bring it up. Consider that we are just noticing some things from, well, a "different perspective", because of their work, all of it.

Mostly, right now, we have a lot more questions than answers. This is typical, and especially when beginning to chart and create new paths in new terrain.

- **Consider skin as communicator of emotion, as much as and usually more quickly, and without as much chance of concealment, than verbal speech.[4] This shows, by simple phenomenology, the signaling and the coordination between nerves, part of the ANS, going from the brain (basal ganglia and other sources?) to the micro-capillaries of the dermis and epidermis, in a number of specific and obvious regions of the body, and the coordination of this with vasodilation and vasconstriction "technology" - the biomechanics of making this work and in a concerted and efficient manner.**

- **Consider skin as sensor of many inputs, not only heat and cold, and how the signaling is different depending upon very slight variations in both degree (amplitude of the signal, not only about temperatures) and location, and how the reactions, both instinctive/autonomic and voluntary/somatic, vary, often incredibly.**

  (Do you ever react with some mild shock, surprise, maybe an "Ouch!" when something happens, a bump or hit, a sharp change in temperature, etc., and then you realize, oh, it did not hurt after all, it was not anything bad, but it was … expected to maybe be different…)

- **What are the consequences, in terms of syndromic conditions such as MALS, POTS, EDS, MFS, hyper/hypo-mobility particularly, and then, think further about hypertension, vasodilation, and arrhythmic disorders, from chronic positional tension and distortion, including in how people sit, lay, walk, move their limbs and torso, and the TENSION within abdominal muscles, within self-restricted breathing (insufficient breaths, poor inhalation and exhalation, also hyperventilation, etc.)?**

- **What are the effects in such syndromes from years – Years, starting in childhood and most definitely emerging in adolescence – of instinctively repressed, withheld, tightened body postures, particularly in the thoracic regions, involving lungs, heart, and the whole of the GI and reproductive tracts – and linked with the noise, irritation, over-caution, fear of irritation, anxiety of being chronically, day in and day out, 7x24, "in" hostile, uncertain, emotionally-charged environments at home, in school, in the streets, in the social centers?**

- **Noise, abusive people, potential and even known specific predators, the increasingly omnipresent anxieties about violation, abuse, rape, eyes and words that are effectively like violence and rape, the "unknowners" with guns, all of that?**

The objective here is not to paint a picture of "anytown, anycountry" as being like certain parts of Chicago or Rio de Janiero. The objective is to state, emphatically, that from the combination of how people are living in their average, typical, anywhere homes, streets, schools, in all those anycountry places, but especially in certain ones, there is a serious situation of psychological stressors that absolutely give rise to neuro-electrochemical stressors, with some of the results being

<u>deformations</u> in all those connective, supportive tissues listed earlier.

4 Granted, this does not happen so much now, with typical modern-day internet-only chatting or old-fashioned phone or in our latest world-change of wearing a lot of masks.

All of these deformations have a role in shaping how we Are, internally as well as externally. All of them have a causative role in how our blood vessels and our "central organs", especially those involving the Flow of nutrients, both O2 and all the rest, throughout our entire body, do literally Shape Themselves and then how they handle, in a basic *tribological* manner, the flow of those fluids, gasses and semi-solid materials, through what have often become contorted, twisted, constricted and rigid vessels.

We believe that what has just been described, in plain English, in non-technical language, is a good starting point for asking the questions about how these deformative processes lead to the kinds of disorders and diseases listed repetitively in these Notes, and how we can think about the ways that genes are activated and deactivated, adversely in long-term effects, and how this results in inflammation both literal and phenomenologically similar, and how we can do something, as physicians and therapists, to detect the problems earlier and cure the problems better.

There is a growing body of clinical evidence, supported by experimental research. This needs to be examined in greater detail from these wholistic perspectives. [12] [14] [15] [16] [17] [20]

§ 4 COVID-19 and Cardiopulmonary Inflammation

Some of these notes, which come from an earlier (December 202) pre-publication set of notes, an "extended abstract and summary" piece, are repeated here because of the importance of bringing up the whole matter of inflammation (connected with a viral infectious disease in this case, but applicable, we feel, to other inflammatory phenomena), with the very central, ubiquitous, fundamental metabolic cycle of Ang, Ang II, ACE and ACE-2. While that biochemical cycle is not the only one of interest with respect to inflammation and other degenerative consequences from both infections and internally-generated triggers of inflammation, it is an important one and it can serve as a model and a pointer for what we can find with other pathways.

Think, please, "outside the box" here a bit, about what biochemical mechanisms are at work in the inflammatory-like world of psychological aggravation, abuse, anxiety, depression, and trauma! There is something similar going on, and we do not employ, over history and across virtually all cultural differences, such similar Language (e.g., "inflame", "inflammatory", "fiery", "explosive", etc.) for no reason!

Consider first some points about COVID-19 and **cardiopulmonary inflammation, then other aspects of autoimmune action and inflammation.**

4.1
Roles of autoimmunity in pulmonary and other organ inflammation, triggered initially by COVID-19, then proceeding in a non-viral-sustained degradation of vascular and alveolar tissues.

Exacerbated inflammation following peak and then fall in viral density: inflammation rises *after* drop in viral density. It is suggested that autoimmune action results in reduction of critical normal, regular, sustained restorative functions in pulmonary vasculature, in the integrity of microcapillaries and in sustainment of alveolar walls, the failure of which includes hypoxia and in combination with hypercarbia,

ARDS is one major consequence. [1]

This sets the stage for what is essentially a positive feedback loop: pulmonary edema, then overload upon a high-probability already weakened heart (various, from myocarditis to arrhythmias, to exacerbation of atherosclerotic, thrombotic, and other conditions). There is less oxygen delivered to the heart as well from the general hypoxia. Consider also back-surges and turbulence in the four pulmonary veins from the failing (and probably AFIB) heart (e.g., progressive failures with left atrium, mitral valve) and the outcome rapidly deteriorates.

This multimodal complex ties in with the findings by David Lee et al of higher levels of anti-Annexin-A2 in patients at risk of and in factual outcome of mortality from COVID-19 hospitalization. [1]

4.2
Mast Cell Activation Syndrome relations with PASC.

Svetlana Blitshteyn et al have brought attention to the matter from somewhat different directions. [2]

- initiation and/or exacerbation of pre-existing POTS following COVID-19, qualitative (at least) indicators of allergy increases in type and intensity
- potential that PASC in some way activates aberrant mast cells, the consequences of which can lead to autoimmune-type reactions in different organ tissues, particularly cardiac muscle. (Cardiac MRI in post-COVID has shown abnormalities in upwards of 78% of 100 patients in one study.) [3]

4.3
Inflammation and cytokine storms with COVID-19.

Feigenbaum and June make several points, in a December 2020 paper (relatively early in the COVID-19 timeline) [4], which are worth quoting here, as jumping-off points for discussion, particularly in the light of work by Lee et all mentioned above in 2.1, and further below in § 3 regarding the ACE2 and the ANG pathways, very important in SARS-CoV-2 infection lifecycle:

> "...reports of hemophagocytosis and elevated cytokine levels — as well as beneficial effects of immunosuppressant agents — in affected patients, particularly those who are the most severely ill, suggest that cytokine storm may contribute to the pathogenesis of Covid-19."
>
> "Serum cytokine levels that are elevated in patients with Covid-19–associated cytokine storm include interleukin-1β, interleukin-6, IP-10, TNF, interferon-γ, macrophage inflammatory protein (MIP) 1α and 1β, and VEGF."
>
> "The correlation between the nasopharyngeal viral load and cytokine levels (e.g., interferon-α, interferon-γ, and TNF), as well as a declining viral load in moderate but not severe cases, suggests that the immune response is positively associated with the viral burden."
>
> "Another hypothesized mechanism involves autoimmunity due to molecular mimicry between SARS-CoV-2 and a self-antigen. ... Patients with multisystem inflammatory syndrome very clearly meet the definition of cytokine storm, since SARS-CoV-2 is no longer present; however, it is unclear whether the cytokine storm is a driver of Covid-19 or a secondary process."
>
> "...cytokine storm triggered by infection with SARS-CoV-2 may require different therapies from those used for cytokine storm due to other causes. Cytokines may be both a key component of the cytokine storm and an essential factor in the antimicrobial response. Thus, blocking

> cytokine signaling may actually impair clearance of SARS-CoV-2, increase the risk of secondary infections, and lead to worse outcomes, as seen with influenza virus."

Finally, the authors point out the caveat for the "should be (have been) obvious" warning signs concerning rapid introduction of different drugs for COVID-19:

> "Despite unknowns regarding the role of immune dysregulation and cytokine storm in Covid-19, hundreds of immunomodulatory drugs are currently under investigation."

(All these quotations are from ref. [4]).

Gotfred-Cato et al address similar concerns, within the context of pediatric multisystem inflammatory syndrome (MIS), in [5].

The stage is set for considering how some of this inflammation is generated and sustained, and particularly also for the case of lung tissue (as pointed out by Lee et al in [1]. Could there be contributors to the inflammatory extremes that originate in either or both of:

- the reduction in certain normal chemistry due to bindings with viruses in the course of viral entry into host cells
- the reduction in certain normal chemistry due to medications administered to counteract those molecules, in an understandable attempt to reduce viral entry by disruption of key receptor bindings?

§ 5 Recap and More Questions and Challenges

Let's review for a moment. We are trying to find the common roots and overlaps between:

5.1

{1} Infectious diseases and other fundamental stressor agents and exposures
{2} Inflammations in response to {1}
{3} Autoimmune Disorders in response to {2}
{4} Autonomic Dysfunctions in response to {1} {2} {3}
{5} Neuro-Cardio-Gastrointestinal Turbulence and Arrhythmia in response to {3} {4}
{6} Psychological stressor agents as an important contributor to {1} {2} {3} {4} {5}

5.2

Reviewing some outstanding questions that need to be answered in order to address 5.1 but which may be answerable in the process of doing 5.1:

⧫ Why inflammation gets out of control – what are the common stimulus factors?
⧫ What may be genetic dispositions – why certain persons and certain organ tissues and regions?

Suggestion – this is not necessarily due to past/present high density of viruses, bacteria or other active pathogens, but to "something more".

♦ How inflammation leads to autoimmune over-reactions

This leads to thoughts about control systems, and bio-cybernetics. Over-compensation with respect to naturally defined boundary conditions, limits and bounds of the operating state-space. Pushing past the limits can lead into what are mathematically called catastrophe functions. [8] Going past the limits, going "out of bounds" literally, can lead in a biological system to not being able to recover, not being able to get back "in bounds" of the state-space. As with getting too far "out of bounds" in driving a vehicle on some hairpin road, or flying a plane and losing control, or causing the ship to capsize - that all translates to one thing – end of the life process.

§ 6 Why the PHEBR and why it is so critical for this area of Complex Medicine

FIRST

A short intro to the concept of **"Complex Medicine"** *a la* complex systems, complex system dynamics, complexity theory.

There is an established science of complexity. Complex systems theory, and the computational modeling thereof. The understanding that complexity is different from complication and "complicated systems" and the perspective that there are such processes which can best be described as self-organizing, emergent, and even non-algorithmic, has a long history [21]. Complexity is different from complicated, although they can surely go together (e.g., a microprocessor is complicated, an automobile or airplane is complicated, but neither is "complex" in the way that a cell or a tree or cat or human is complex, but there can be complexity in machines and complicatedness in biological organisms, certainly).

Complex systems are studied in physics, chemistry, biology, social sciences, economics. It seems appropriate that we recognize and give attention to a domain of problems within medicine – within the study of the etiology and therapy for dysfunction and disease within the living organism – that qualify as being "Complex Medicine". This certainly is going to take some serious dialog and discussion.[5]

What are some of the characteristics, going forward, for the study-discipline of **Complex Medicine**?

- Causal relations, precursors, codependencies, side-effects, contraindicators, involved in number of conditions that are typically labeled as "syndromes" up to the present

- Diseases and symdromic phenomena that are often, at least up to the recent past (and too often, still in mainstream clinical medical practice) labeled as "psychological disturbance, all in the head, go see a psychologist and get some anti-depressants" - this sounds curt and harsh, but it is what happens a lot to many, particularly with ME, CFS, MALS, POTS.

5 Can a group of us, meaning here, readers of this and communicator/collaborators together, band together and create an actual conference – both onsite and online – in, say, a place like Florida, for instance, and work together on refining and defining "Complex Medicine" - but not only in the abstract realm, but concretely, clinically-focused, therapy-focused, in the areas of symptomology brought up here in this "white paper"? Let's try to Do It Together!

- Applying theoretic and mathematical methods and models from formal complexity theory, from complex systems in the abstract, from complex systems in other branches of the natural world, to medicine and, again, toward some of the conditions that are the topics covered in this "white paper"

- Seeking some "common denominators" that are, hopefully, discernable and describable in terms of the metabolic pathways of:

  neural signals reaching tissues such as muscle and connective tissues of the cardiovascular network, and regions prone to and subject to inflammatory response, and leading to specific protein chemistry that in turn causes activation or deactivation of specific genes, affecting in turn other protein production, and thus contributing to those positive feedback loops which longer-term give rise to the syndromic problems that become chronic and in some cases lethal.

This is not short-term and it requires several minds coming together and hammering out, carving out, sculpting the marble, together.

Also, this type of undertaking or refocusing requires a lot more data, exactly of the type that the Population Gealth Equity Bioinformatics Resource (PHEBR) has and will bring together.

More needs to be stated here pertaining to the PHEBR, since it is integral for assimilating a much larger and more rigorous, reliable dataset about actual patient quantitative and qualitative histories that can aid in addressing the infection-stress-inflammation-autoimmune cycle. (This section (§ 6.1 – 6.5) is taken from the previous Dec. 2021 NPC summary.)

6.1

The PHEBR will serve many different medical spheres of interest that span research, experiment and clinical services. These include computational (modeling, simulation, and dissemination) capabilities for:

- analysis of deficits and development of methods (mechanisms, procedures) for removing deficits in diagnostics and early detection of disorders and diseases:
  - cardiovascular and dysautonomic disorders as the primary focus
  - autoimmune diseases including multiple sclerosis (MS), Alzheimer's, Parkinson's, Lupus, which are particularly challenging to detect, particularly in early-onset or pre-onset stages, in general, among any and all populations, and for which many minority populations are receiving inadequate diagnostic and preventive medical care including education as well as prophylactic/therapeutic treatments.

- analysis of deficits and development of methods for improving day-to-day and long-term care of patients afflicted with such disorders (i.e., removing deficits in long-term care of persons with physical and mental disabilities that prevent or reduce dramatically the person's ability for self-mobility (e.g., walking), self-care (e.g., household, personal), and social interactions).

6.2

Within the PHEBR there is extensive employment of synthetic intelligence ("SI", aka "AI") algorithms, and the primary applications are in:

- decisions regarding authenticity and usability of data elements
- inferences where data is incomplete, sketchy, and unambiguous
- natural language understanding for data originating as text descriptions

- inferences regarding sources for new data on patients and patient group types that should be obtained
- inferences including forecasts for symptoms and specific pathologies to be targets of examination and diagnostics including by empirical, instrumental forms of measurement and evaluation

6.3

The central component of the SI technology used within the PHEBR is known as Seldon. This is a composite of pattern recognition, inference and predictive software developed over a period of years by members of the TETRAD collaborative research team. Seldon has been designed for large datasets with high degrees of uncertain, incomplete and conflicting data.

6.4

The PHEBR includes data pertinent to the following (which constitute the focus of a current, long-term, multi-institutional, international consortium in which M J Dudziak and TETRAD are involved, serving as principal investigator and institution ("Neuroplex-C"):

- Cardiomyopathies[6] including but not limited to progressed development of arrhythmias such as tachycardia and AFIB
- Myocarditis and periocarditis, and consequent cardiomuscular disorders linked with infectious diseases and/or other forms of inflammatory disease, including but not limited to COVID-19
- POTS (postural orthostatic tachycardia syndrome)
- MALS (median arcurate ligament syndrome)
- EDS and hyperelasticity within the arterial network and particularly the aorta
- Hypertension, atherosclerosis and myocardial infarction
- Gastrointestinal disorders (such as IBS, POI and Crohn's) linked with the above, particularly POTS
- Dysautonomic disorders which are viewed as being related in causal and/or concomitant relations with one or more of the cardiac dysfunctions listed above
- Psychological disorders linked with several of the above conditions, particularly PTSD and depression)
- Special attention to disorders with both neurophysiological components that are associated with the following areas of investigation:
  - chronic pain
  - post-surgical trauma including development of adhesions affecting cardiovascular, gastrointestinal and urological organs
  - psychological reactions including development of dependencies upon addictive substances

6.5

The PHEBR meets clear and consensus-agreed needs expressed within the medical communities focused upon these categories of disorder and disease. PHEBR provides new, systematic, thorough, and large-scale bioinformatics and supports the subsequent development of useful large-population medical databases, covering precisely the disorder and disease topics listed above. PHEBR can be used within academic, public-sector, and corporate (e.g., pharmaceutical industry) sectors for:

- healthcare planning by all types of provider professionals and institutions
- pharmaceutical design and development

6 Dilated (DCM), hypertrophic (HCM), restrictive (RCM and left-ventricular non-compaction (LVNC), with particular attention to the other conditions, disorders and diseases referenced above in this proposal context

- medical device design and development
- pregnancy and postpartum healthcare
- long-term healthcare
- social services for the disabled
- public health education for the general population, especially youth

§ 7 More Background and References

Additional background information including references, bibliographies, and matters of contractual and other formal natures, is available. The next step is to begin meetings and discussions, commencing via teleconference and then is appropriate, let's meet in person, with the potential for seminars and lectures serving students, colleagues, others.

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Additional information resources including a very large bibliography can be found at:
www.neuroplex-c.tdyn.org

§ A Appendix

Now consider some other important pathways in the development of COVID-19 pertaining to the viral replication, and specifically the critical steps of **attachment and penetration (leaving aside for the moment the uncoating, replication, assembly, and release procedures).**

A 1 Inflammation, ACE2, COVID

A 1.1 S1 and S2 spike proteins and ACE2 receptors.

For SARS-CoV-2, this centers upon the actions of the S1 and S2 protein components of the coronavirus spikes, and this involves the S-glycoproteins binding to the receptor Angiotensin-Converting Enzyme 2 (ACE2). Break this cycle and the virus cannot gain entry to host cells, replication is curtailed, viral density drops, and the disease will presumably have a short lifecycle.

How to accomplish this goal? The usual thinking, for well over a century and a half, about how to do this involves production of antibodies through one of two ways: the body's own mechanisms due to prior infections, or the use of vaccines.

Let's put all vaccine thinking aside for the moment. Vaccines are effective, and while there may be (usually, only) extraordinarily low incidences of complications – some of which connect with self-antigens and molecular look-alikes to the target pathogen molecules of interest – there is no evidence that vaccines lead to the kinds of inflammations and also autoimmune-type reactions that are being seen in diseases like COVID-19 including PASC.

Let's consider two types of antiviral tactics:

(1) the use of pharmacological agents that will be ACE2 inhibitors
(2) the use (still hypothetical, to date) of a radically different approach to virus "mechanics" and the disruption of the viral process that (in the case of SARS-CoV-2) would obviate the need for ACE2 inhibitors to block the spike protein "algorithm of molecular unwinding" that enables the first stage of viral entry to initiate.

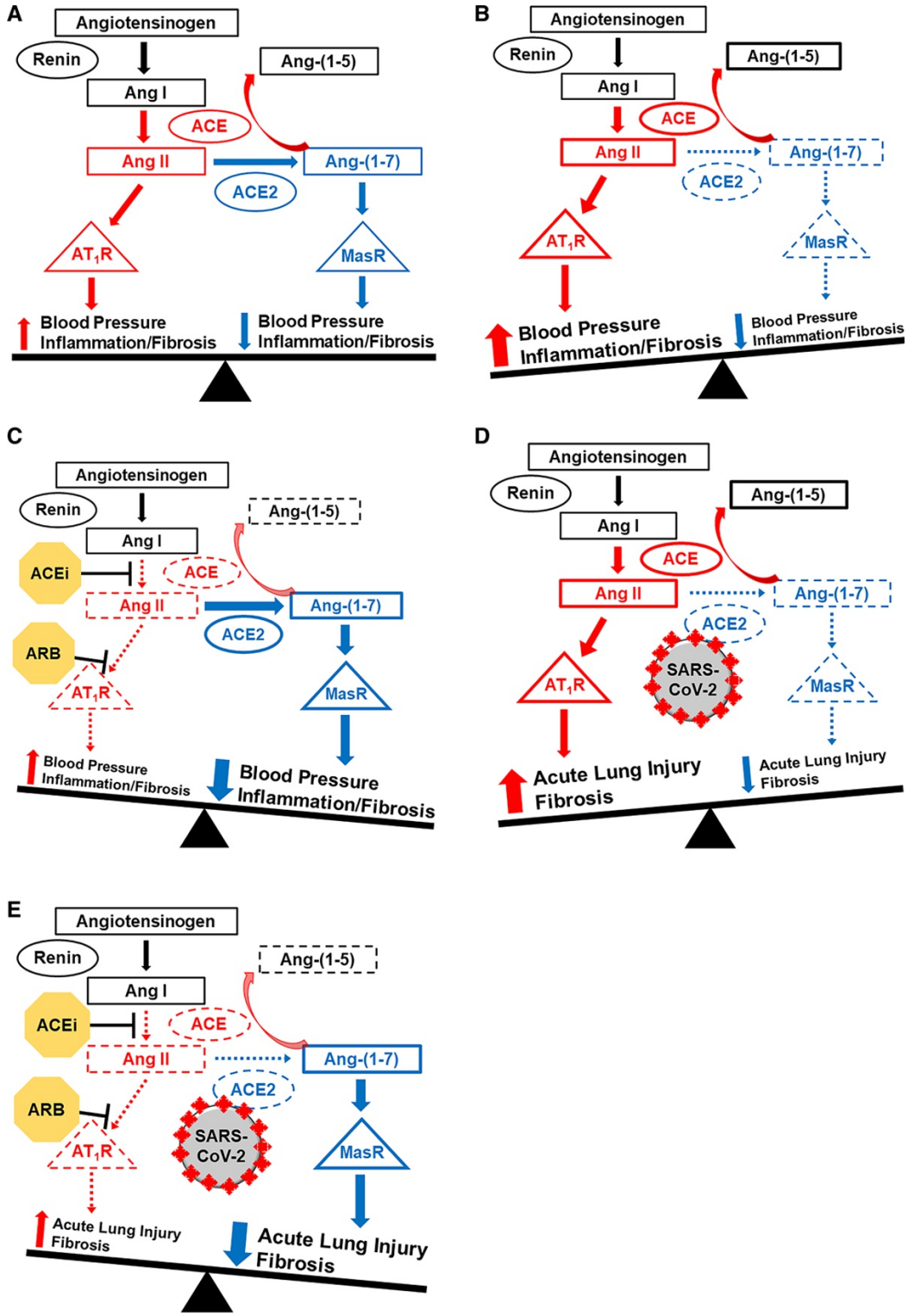
Option 1 is something in the current repertoire of medicine, and it is our concern here because of potential links with the increase of inflammation, fibrosis, and causative/parallel conditions of increased oxidative stress, Na+ and H2O re-absorption/retention, sympathetic nervous system (SNS) tone, and vasoconstriction.

Option 2 does not yet exist but is the subject of a research project underway since early 2020, since the very first indications of COVID-19 as a potential epidemic and pandemic. (We will return to Option 2 later on in these notes.)

A 1.2 Ang II, ACE, ACE2, and CE2 inhibitors.

Figure 1 on the next page illustrates key dynamics of Ang I → Ang II and with ACE2 → Ang-(1-7). These are important for understanding how changes in these pathways due to the SARC-CoV-2 virus itself and also due to medications given to patients – and also in the case of patients who are regularly taking

various blockers as part of, for instance, a cardiovascular regimen, can be influential in detrimental ways for the outcome of serious comorbidities and life survival after COVID-19.



(from South, Brady, & Flynn [6])

ACE2 transforms Ang II into Ang-(1-7) which leads to vasodilation, reduction of blood pressure, reduction of Na+ and H2O through excretion, reduction of SNS tone, and reduction of inflammation and fibrosis. [7]

ACE acting upon Ang II leads to another path which is quite the opposite – increases in oxidative stress, SNS tone, Na+ and H2O re-absorption/retention, vasoconstriction, and with this, inflammation and fibrosis.

ACE inhibitors and ARB (Ang II receptor blockers) cause a shift to the ACE2 pathway, but this can be detrimental in terms of preventing viral endocytosis and replication.

However(!), ACE2 reduction through two pathways:

- Viral uptake pure and simple
- ACE2-inhibitors for purposes of preventing viral uptake by blocking S1 and S2 spike protein actions with the host cells

will shift to the ACE/Ang II pathway and contribute to inflammation, fibrosis, and the acute lung disease that characterizes advanced COVID-19 and its "long"variant, PASC.

A 1.3 A Challenging Implication:

Could the reduction of ACE2 due to viral action and compounded by ACE2 blocker antiviral-intent medications be what "sets the stage" in the lungs for the following:

- the basic heightened inflammation and fibrosis ("alpha phase") that leads to
- "naturally expectable" autoimmune actions directed against the degraded, inflamed tissues (e.g., alveolar, microcapillary types) – this can be termed "beta phase", that in turn leads to
- excessive autoimmune response which causes the formation of "self-antigens" and self-directed antibody-type actions, of the sort that there is now a full-blow autoimmune response against both the damaged and any similar/adjoining healthy tissue ("gamma phase")?

This "gamma phase" could be what sets up "auto-antibodies" that perform antiphospholipid actions against Annexin A2, for instance.

A 1.4 Goals and More Questions.

Goal: Reduce the onset and intensity of inflammation.
?? Can we quantify what are the effects of the virus "by itself" as distinct from the effects of the inflammatory responses when the latter have become excessive? How can we quantify these differences?

The inflammatory damage seems to be the worse of the two, and (at least in the case of COVID-19) it occurs after the virus is already significantly diminishing its presence within the host.

More questions:
Does a large viral density in the host do as much damage (chronic, comorbidities, lethalities) as an intense post-infection inflammatory storm?

Does a large viral density (strong infection) necessarily cause intense or prolonged inflammation?

7 I need to understand much better the mechanisms by which this process reduces inflammation and fibrosis!

Goal: Find another way besides ACE2 inhibitor drugs to combat viral entry and replication.

This leads us to the second option mentioned earlier (in 3.1):
Disrupting the spike protein dynamics leading to endocytosis by disrupting the viral structure – in the spikes or in the envelope – in such a way as to prevent viral entry, but doing so without chemically attacking any receptors (like ACE2) and also without a vaccine to produce antibodies to specific viral molecular features which could be absent or significantly altered through a viral genetic mutation, thereby rendering the vaccine either useless or reduced in effectiveness. This is something we have seen happen time and time again with influenza and other viruses, and now with SARS-CoV-2 in particular.

We want to not interfere with ACE2, and we do not want to increase the ACE → Ang II metabolics, because that leads to increased inflammation and fibrosis.

This approach could also mitigate the problem of anti-antibodies working against Annexin A2.

A 2 VESID

A 2.1

The VESID antiviral approach. --- this is in the earlier document from mid-December, the one just prior to this in fact, for NPC work. However, think about:

How VESID thinking can apply to what needs to be done to combat neuro electrochem stressor agents and their actions in degrading certain cellular tissues and causing inflammatory response and autoimmune response.

A 2.2

VESID = Viral Entry Structural Integrity Disruption.
The whole model is based upon topology and how to weaken a geometrical object by one of two ways, abstractly:

- loosen and soften it in certain critical points where there are joins that, if broken easily, too easily, too early, will change the topology and the ability of the object to "do certain geometrical operations" - in the case of a virus, these include the operations involved, with either spikes or envelope portions, or anywhere, that are needed for viral entry into a host cell.
  OR
- tighten and harden it in certain critical points, for the same objective results

Thus, make it

- "soft, mushy, pliable", like a football (soccer ball) that is under-inflated or torn.
  OR
- Make it "stiff, brittle, rigid", like an over-inflated football.

Either way, you can't play a good game with a bad ball.

There is a lot of information about VESID, in other papers, notes, reports, presentations. See [7].

Figures 2-7 on the following pages gives some indications of the topological deformation/reformation approach. The process is through a yet-to-be-finalized pharmaceutical agent that can be administered orally or nasally, in order to act upon early-entrant viruses before and in their passage to lower respiratory tracts. Note that such drug or drugs are not intended to act as antibodies nor as receptor blockers but purely through reactions including bindings with proteins or lipid-protein-carbohydrate structure in the spikes and/or envelopes, and once again, focusing upon the "join" regions of the viral topology.

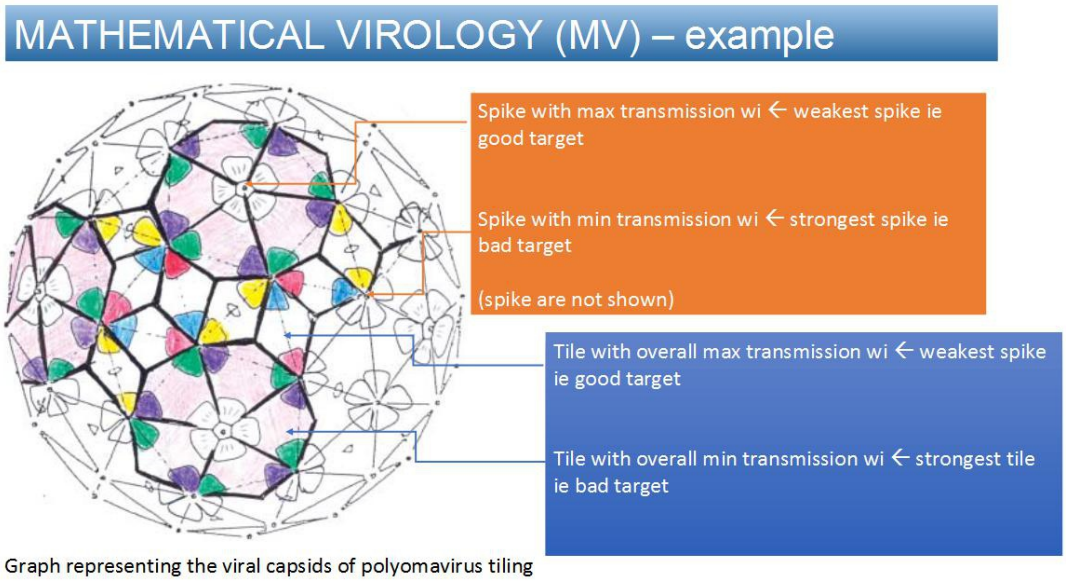


Figure 2

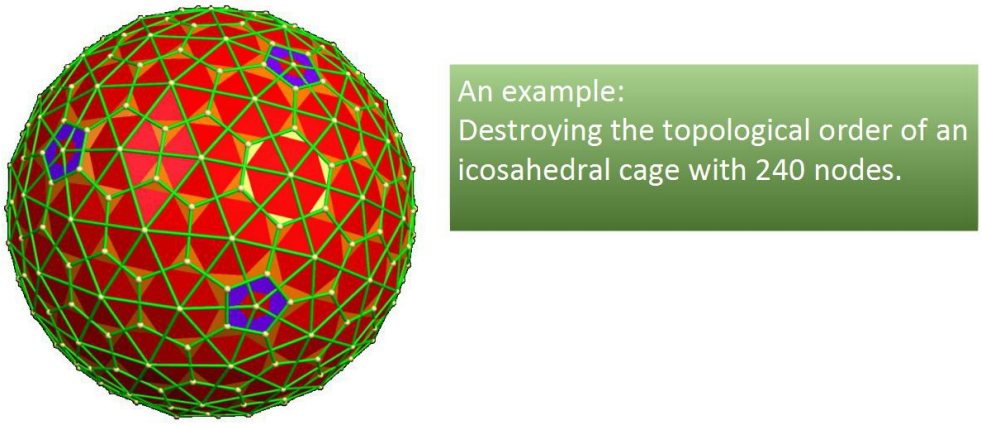


Figure 3

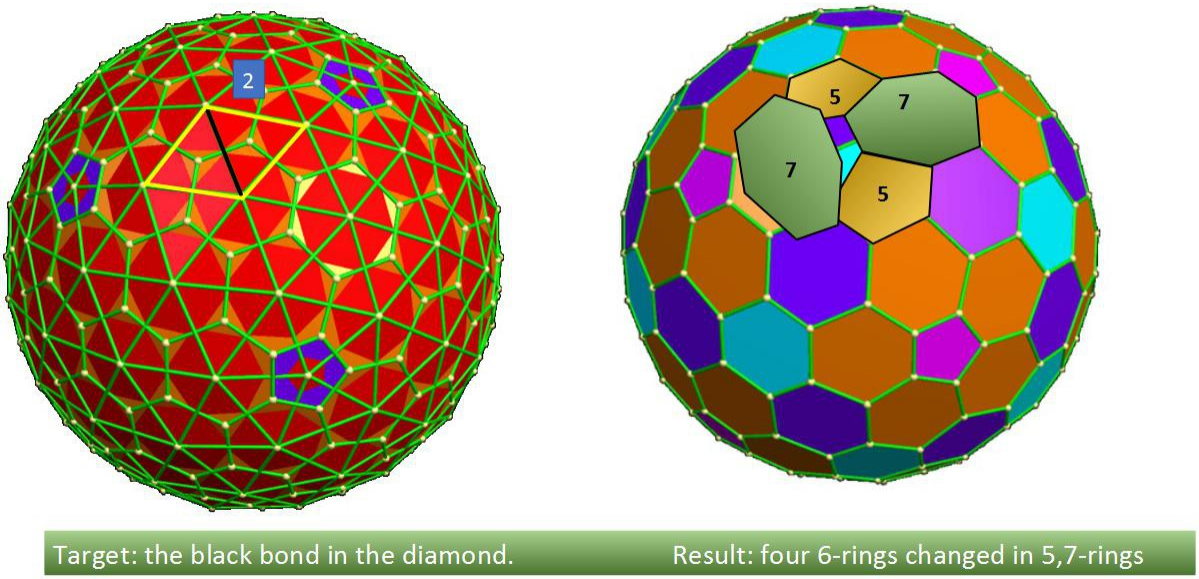


Figure 4

By rotating the proper bonds the iteration of SW created a zipper-like region of 6|6 pairs that separates the original 5|7 pairs.

This cage remains with a couple of topological damages:

i) Globally, it has a topological symmetry that in respect to the original organization is "broken" so this "organism" is surely less effective in its functionalities; we may think to the gray tiles as signs of the damages on the virus surface;

ii) Locally, there are an increased number of weak bonds or nodes (this concept is measurable by computing the proper topological descriptors)

Now consider what this abstraction can be in terms of a virus such as SARS-CoV-2 (next page--->>>)

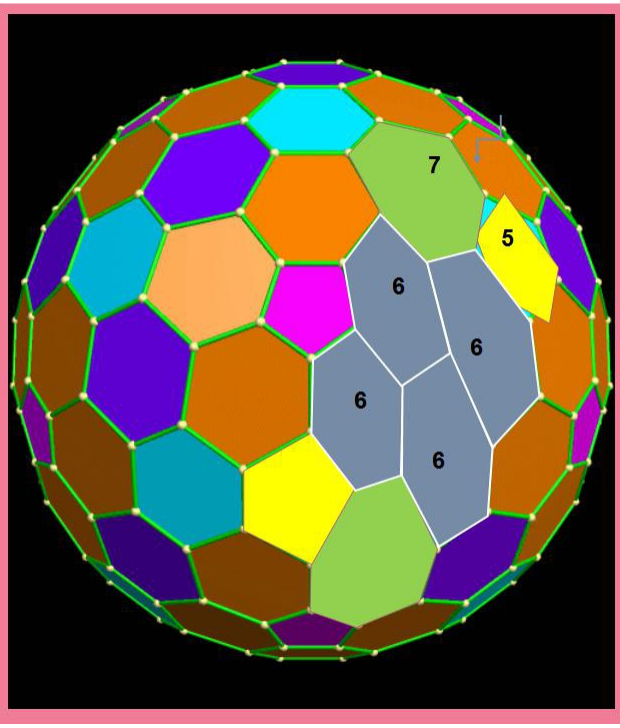


Figure 5

We conjecture that there can be created two results in favor of object (e.g., virus) topological destabilization and consequent metabolic (infective) destabilization.

[1] Within the zipper-like region of 6|6 pairs (or "quad" of such hexagons) that separates the original 5|7 pairs, this "cage", having a broken/damaged topological symmetry, will degrade the stability, possibly the cleavage, possibly the RNA-coupled viral entry by the S2 spike component, into a host cell membrane.

[2] This disruption among the tile structure may serve to "throw" the viral spherical containment entity into a "decoherence" state, with respect to what we speculate may exist, in many viral and cellular structures, in terms of large-scale, macromolecular, entanglement states. Granted, such entanglement and coherence is highly theoretical and speculative at present. However, there may be other forms of topological ordering and efficiency of energy transport, including the common biological roles of biosolitons (e.g., observations with intracellular filaments, actin, microtubulin, and DNA). We suspect that there are biosoliton wave dynamics involved in viral as well as eukaryotic and bacterial cell molecular processes, and that the disruption of the normal biosoliton mechanics can lead to disruption of the virus ability to "squeeze and protrude" the extension of an S2 protein segment, with viral RNA attached, into a bonding and envelopment position with a cell membrane and thus subsequent cell entry, lysosome activity, subsequent release, and then viral RNA operations leading to new viral assembly, construction and release out of the host cell.

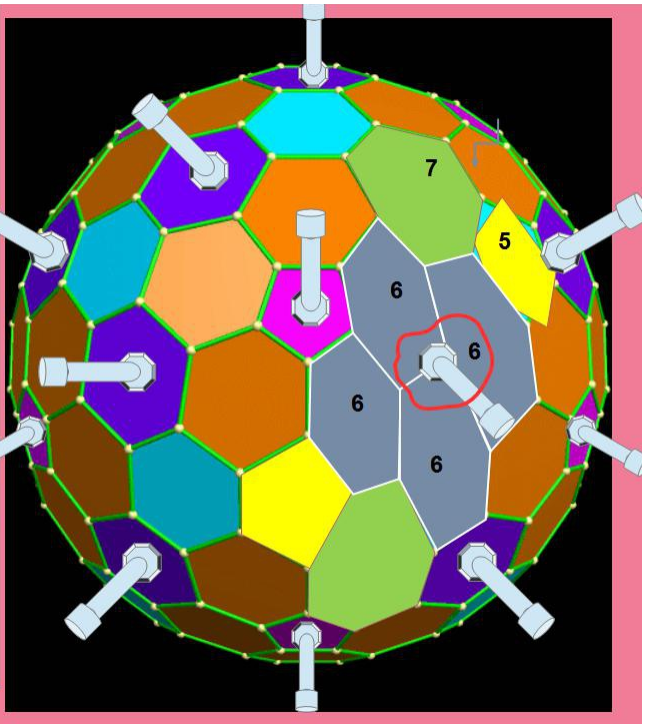


Figure 6

Thus we want to have the damage and destabilization (indicated by the red wavy line) to be ideally replicated across the surface of the virus. The "programmatically" (algorithmically) broken virus will then have its own "softrware bug" that will render it harmless, to be swept away as intercellular garbage.

Now, the objective is to find one or more drug molecules which, in the context of the MACE ("coronaligans" operating concept) therapy, will create the Desired Topological Defects in the virus.

Such drug(s) must ideally bind with the S1 or directly with the S2 components of the viral spikes (in the cse of SARS-CoV-2 and related virus types).

This brings us directly back to the original MACE design concepts and proposed methods.

However, we could also consider some drug or drug combination that, delivered in a MACE protocol (e.g., with a PDMS gel pseudo-c contained in a spray, syrup or other oral/nasal format), will directly damage portions of the viral surface structure – in particular the base units that establish "tile-like" components of the viral main surface, or those portions to which the S1+S2 spikes are attached prior to any cleavage processes.

[This is the final slide in the set as of 27.mar.2020, 15:00 EDT, mjd]

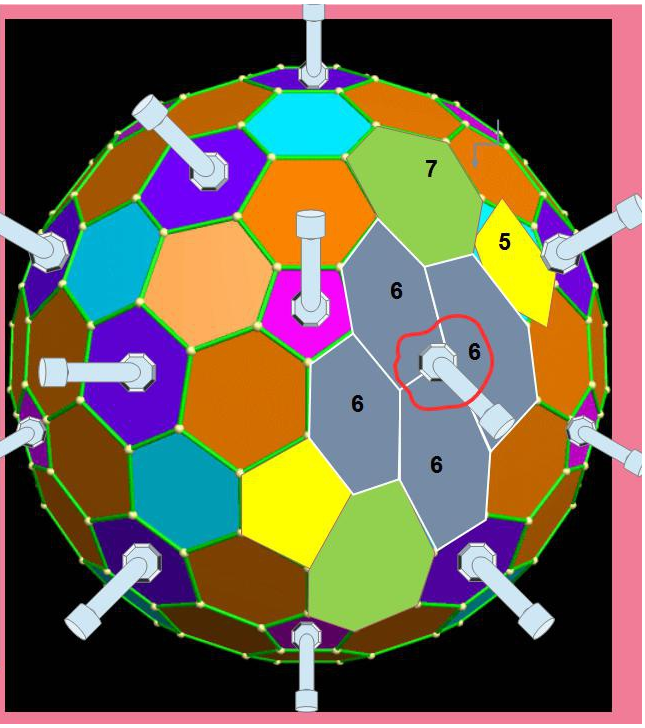


Figure 7

A 2.3

VESID objectives.

The VESID goals may be summarized in this way, as contributing to a reduction of the metabolism that exacerbates inflammation within and after viral exposure (using COVID-19 as the primary example and current focus).

{I}
Inhibit ACE2 in and only in viral spike decomposition process, and not elsewhere in the host organism (obviously an "ideal" to be stated)

OR

{II}
Disrupt viral spike dynamics in some other way.
Prevent S1-S2 spike protein dynamics by "over-tightening" or "loosening" bonds and thus the topological structure, within the spike itself (e.g., between S1 and S2).

OR

{III}
Effect the over-tightening or loosening at the "join" lines between the spikes and the envelope substructure of the virus.

OR

{IV}
Effect over-tightening or loosening of other viral envelope components, other than those connecting with the spikes.

A 3 Active and Potential Collaborators

A 3.1

Who (where) are the people who, from the perspective of the Neuroplex-C team, have special and outstanding and critical things of value for all of thus? These include and may (should?!) include:

Among USA persons/institutions:

Johns Hopkins University	New York Univ.
Columbia Univ.	Vanderbilt Univ.
Univ. of Florida	Univ. of Miami
Mayo Clinic	Texas Heart Institute
Meharry Medical College	Emory Univ.
Florida State Univ.	Dysautonomia International

and several private healthcare and pharmaceutical corporations

Among global persons/institutions:

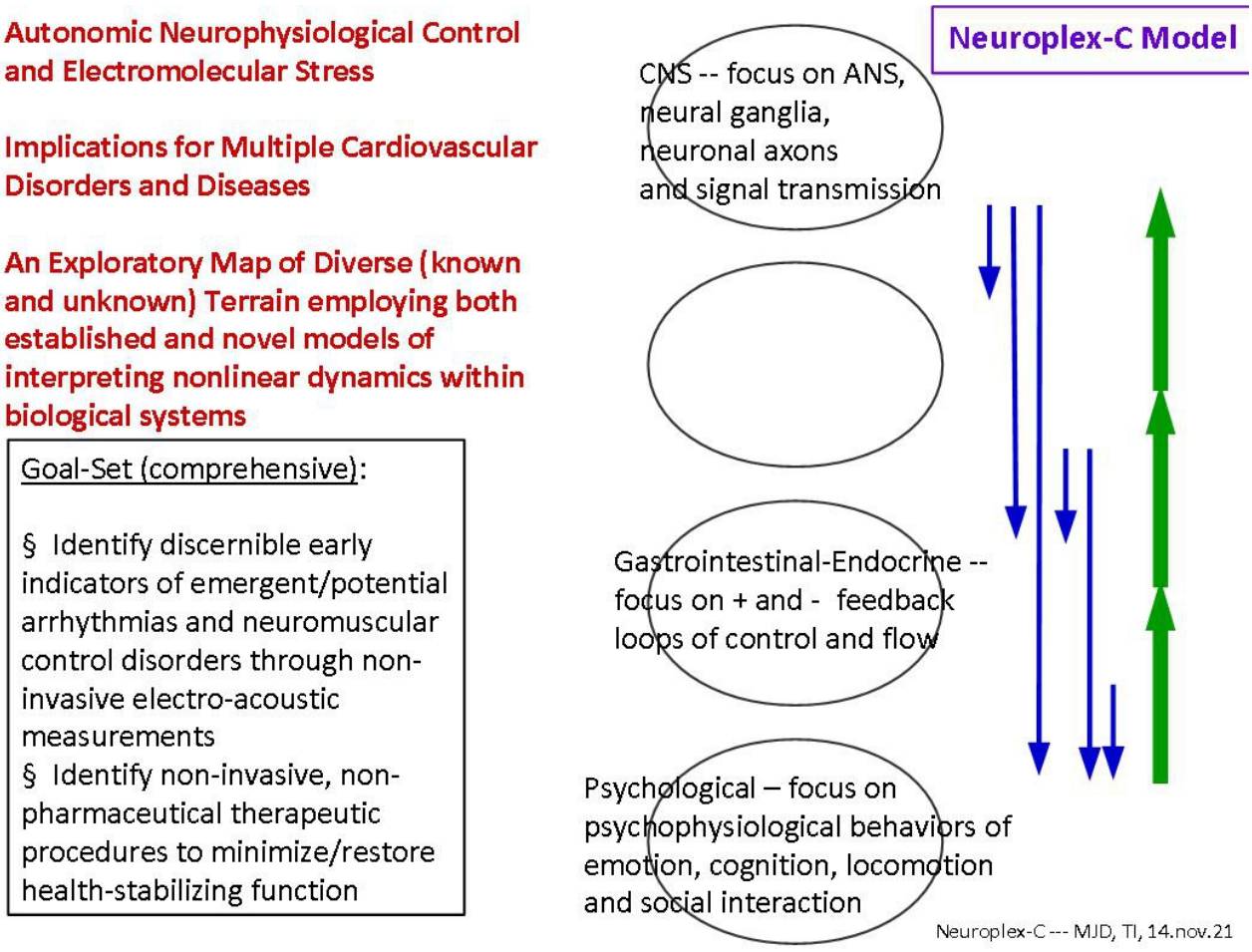
Norwegian Univ. of Science and Technology	Brighton Univ. (UK)

Oslo Univ. (NO) Karolinska Institute (SE)
Göttingen Univ. (DE) Durham Univ. (UK)
Max Planck Institute for Dynamics and Self-Organization (DE)
German Center for Cardiovascular Research (DE)
and several private healthcare and pharmaceutical corporations

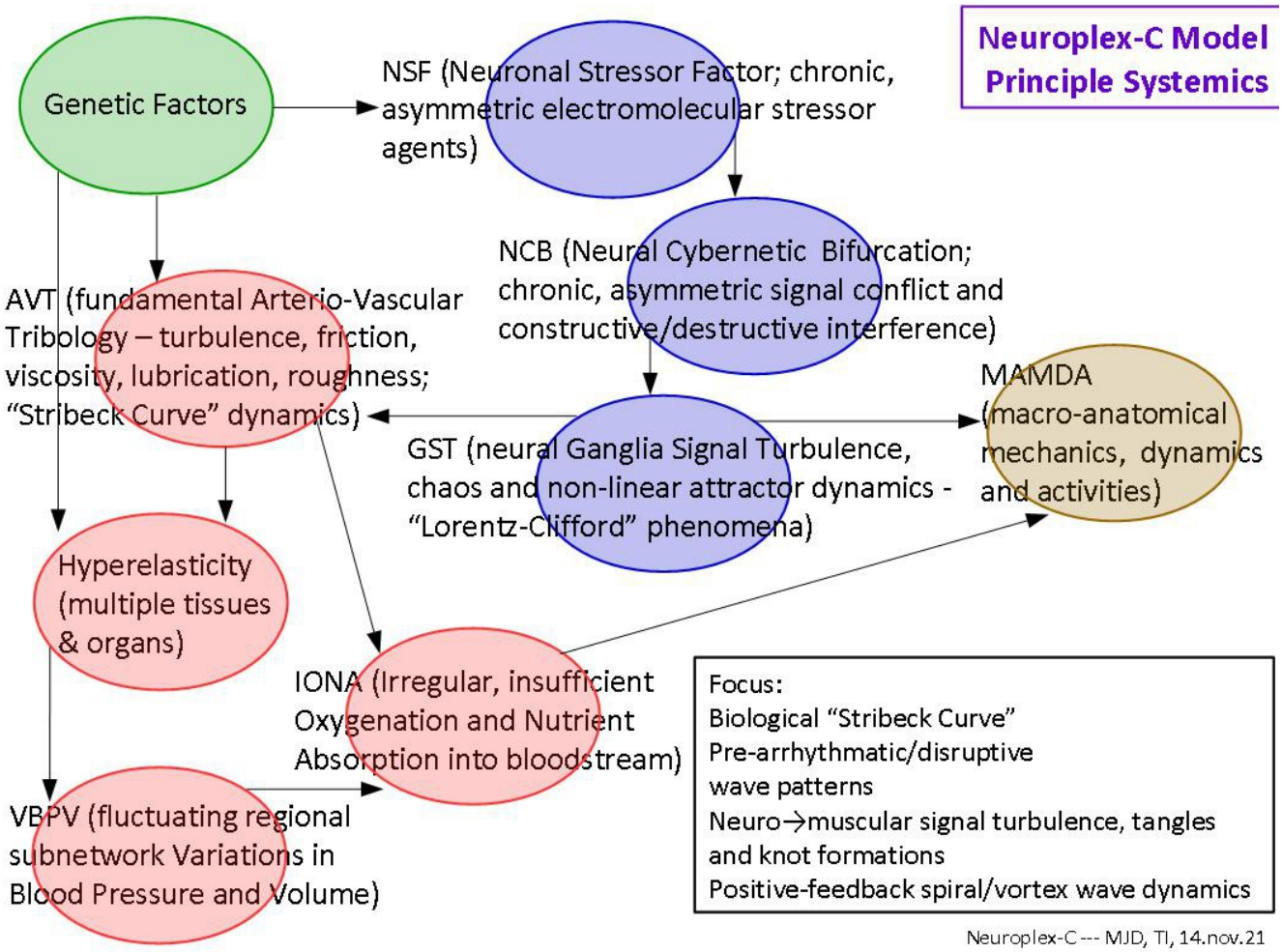
Note that in most cases, there may be zero funding requirements, or a very modest consulting arrangement, for most of these institutions and their involvement, because of other ongoing support mechanisms already in place or confirmed otherwise.

A 4 Two Earlier Diagrams

These three figures (from November 2021), below and on the following page, provide illustrations of the basic theoretical framework, leading up to what is then presented in more detail in Figures 1-4 in the main text (Section § 2 – Introduction).



A 4 -- Figure 1



A 4 -- Figure 2

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