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SLE classification criteria: Is "The causality principle" integrated and operative – and do the molecular and genetical network, on which criteria depend on, support the definition of SLE as "a one disease entity" – A theoretical discussion

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ABSTRACT

Molecular and cellular aspects of the autoimmune pathophysiology in SLE is linked to the "The causality principle". SLE Classification Criteria identify per definition disease measures (here: synonymous with classification criteria), but not diagnostic criteria within a classical framework. These two mostly theoretical criteria collections represent a salient conflict between phenomenology and the causality principle – between disease measures and molecular interactions that promote such measures, in other words their cause(s). Essentially, each criterion evolves from immunogenic and inflammatory signals – some are interconnected, some are not. Disparate signals instigated by disparate causes. These may promote clinically heterogenous SLE cohorts with respect to organ affection, autoimmunity, and disease course. There is today no concise measures or arguments that settle whether SLE cohorts evolve from one decisive etiological factor (homogenous cohorts), or if disparate pathobiological factors promote SLE (heterogenous cohorts). Current SLE cohorts are not ideal substrates to serve as study objects if the research aims are to describe *etiology, and molecular interactions that cause - and link - primary and secondary pathophysiological events together* - events that account for early and progressive SLE. We have to develop SLE criteria allowing us to identify definable categories of SLE in order to describe etiology, pathophysiology and diagnostic criteria of delimitated SLE versions. In this regard, the causality principle is central to define dominant etiologies of individual SLE categories, and subsequent and consequent down-stream diagnostic disease measures. In this sense, we may whether we like it or not identify different SLE categories like "genuine SLE" and "SLE-like non-SLE" syndromes. Many aspects of this problem are thoroughly discussed in this study.

Defining the philosophical nature of the problems presented in this study in the words of Werner Heisenberg.[1]

"The positivists have a simple solution: the world must be divided into that which we can say clearly and the rest, which we had better pass over in silence. But can anyone conceive of a more pointless philosophy, seeing that what we can say clearly amounts to next to nothing? If we omitted all that is unclear, we would probably be left with completely uninteresting and trivial tautologies."[2]

1. Introduction

The syndrome SLE is formally defined by classification criteria.

Abbreviations: ANA, antinuclear antibodies; MM, mesangial matrix; GBM, glomerulus basement membranes; SBMZ, skin basement membrane zone; NMDAR, *N*-methyl-D-aspartate receptor (also known as the NMDA receptor NMDAR).

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[1] **Werner Karl Heisenberg** (5 December 1901–1 February 1976) was a German theoretical physicist and one of the main pioneers of *the theory of quantum mechanics*. He is known for the *uncertainty principle*, which he published in 1927. Heisenberg was awarded the 1932 Nobel Prize in Physics "for the creation of quantum mechanics". He was a humanist and of high ethical standard living and working in Nazi Germany.

[2] *Werner Heisenberg, "Positivism, Metaphysics and Religion," The World Treasury of Physics, Astronomy & Mathematics" Ed. T. Ferris (Little, Brown & Co., NY (1991).*

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Practically, the criteria are intimately linked to the attribution rules developed for all SLE classification versions. This principle developed to define SLE is problematic as long as the criteria do not relate to each other in an inner context - a context that is formed by implementation of a sound and understandable (and unifying) causality principle. How can we perform evocative groundbreaking science from this perception and perspective?

There is an identifiable problem when we try to describe a biological connection between SLE classification criteria, SLE categories, and the causality principle. The causality principle states that every effect – here defined as a disease measure or a criterion - has a cause [1–3] that can be dissected down to molecular and genetical levels [4–6]. In their study, Guthridge et al. [6] concluded that "*Molecular profiles distinguish SLE subsets that are not apparent from clinical information. Prospective longitudinal studies of these profiles may help improve prognostic evaluation, clinical trial design, and precision medicine approaches*". This problematizes if SLE, as it is classified today, can be regarded as a disease entity. Rather, SLE should be categorized into subgroups in harmony with observations and ideas presented by Isenberg et al. [7] and Pisetsky et al. [8] . This is discussed in paragraph 4.1.2 later in this study.

Classification criteria represent a cluster of disease measures which are accepted and implemented as criteria that classify SLE – they are all responses to causes – in this context *etiologies*. However, no data have been provided that allow us to conclude that SLE classification criteria evolve as a consequence of *an integrated and dominant* cause. However, according to the attribution rules for the criteria, *all of them matter in the classification process irrespective whether they are observed timely independent from each other or not; whether they are related to each other in a causal pathophysiological network or not; whether they are connected to a defined and unifying etiology or not* [9–12]. Therefore, it is not established whether these criteria evolve from one dominant cause or from disparate causal origins. They do not fit into the unified causality principle concept.

The causality principle may have impact on our still inconsistent definition of SLE at different hierarchical levels:

i. The cause(s) explain(s) consequent, downstream, individual, and interdependent disease measures in SLE;
ii. the cause always precedes the disease measures within a reasonable response time;
iii. the cause is timely preceding primary *and subsequent* (down-stream) disease measures;
iv. one cause may be succeeded by *several events* provided they are connected in a common pathophysiological network. That is, one cause may promote disparate disease measures, and every disease measure may cause new down-stream disease measures. This is discussed in detail below, and may explain disparate phenotypes of SLE even when emerging from one inciting cause.

Thus, the causality principle could serve the general research principle – a testable hypothesis - and guide us through our studies of SLE with a focus on its etiology, pathophysiology, symptomatology - and experimental therapies.

1.1. SLE is a research field that crosses scientific borders and advances innovative and precise concepts and hypotheses, but also inconsistent paradoxes making research results difficult to interpret

The science of SLE is multifaceted and crosses many scientific borders, similar to the complex and combined approaches to e.g. investigate the system science on anthropology. Science on anthropology covers disciplines like human evolution and behavior, biology by all means, cultures, societies, and linguistics, related to both past and present human species (see e.g. reference to biological anthropology [13]).

Like the sophisticated scientific complexity of anthropology, SLE is comparably a scientifically complex and complicated syndrome. We have from studies of SLE learned about epidemiology of SLE and many basic and systemic operational aspects of the immune system, how the immune system work, how it is controlled, and how tolerance is maintained or terminated [14–22]. SLE has been utilized as a model disease to study how inflammation is triggered, and is being a subject as to how the network between complement, cytokines, macrophages, T cells and B cells operate at molecular and cellular levels (see central scientific milestones given in Table 3 in reference [23], and information in [20,24–27]).

Despite extensive and fruitful investigations related to basic and clinical aspects of SLE, the results of these studies have not enabled us to invent an unambiguous, functional and causality-related definition of SLE. If we consider the different scientific parameters, like immunity, repertoire of antibody specificities designed by immunoglobulin variable region genes [19], and their specificities related to pathophysiology, pathology, clinical medicine, and human behavior (the latter deals with problems around cerebral lupus, see [23]), we have still a long way to go to if we will reach an insight necessary to establish a definitive holistic and diagnostic prototype description of the syndrome SLE, and to introduce relevant intricate causal therapy modalities.

The authority of rules ascribed to the use of SLE classification criteria has not supported the insight necessary to explain the poly-phenotypical and pathophysiological nature of the complexity of SLE. We are nevertheless using SLE classification criteria without restrain to unambiguously classify the syndrome for studies of genetics, epidemiology and etiology [28].

Notably, however, classification criteria are disqualified from being used as diagnostic criteria – but in fact, the opposite is true in real life from the following reasons: If the authoritative rules for the classification criteria versions are fulfilled to classify patients as suffering from SLE [29–33], those patients are enrolled into an SLE cohort. Ergo, classification criteria categorize SLE, and if the authoritative rules are completed, the measures are given the authority as conclusive *diagnostic* criteria. Surprisingly, this binary classification model (i.e. have or have not SLE) contribute to establishment of SLE cohorts characterized by highly disparate patients with mild or serious SLE, and SLE with or without nephritis and anti-dsDNA antibodies [12,28,34,35]. This is a principal problem that may directly reduce the impact of SLE-related studies applied to SLE under the designation "a one disease entity".

1.2. SLE classification criteria are selected by implementing three disconnected procedures: Traditions, consensus, statistics – And not by an argumentation that focus on why (or if) the criteria are causally interconnected and linked to etiology(ies) in SLE

There is a significant lack of scientific objectivity adhered to discussions aimed to validate the processes leading to the contemporary SLE classification criteria. According to the original literature on selection of the SLE classification criteria [29–33], the selection processes relied on three corner stones: *i.* expert tradition-related insight (based on their contemporary traditional and established knowledge), *ii.* consensus (discussions and democratic elections of criteria by Delphi panels [36]), *iii.* Statistics (probing the most recent classification criteria against prior classification criteria versions from which many of the actual criteria derive (as e.g. described in [32,33]. None of these procedures ensure exact scientific approaches as defined in the science of nosology [37,38]. Nosology signifies philosophy, interpretations and realities on classification of diseases. A central aspect of nosology is applied to classification of diseases based on *facts*, and to focus on the implementation of etiological and pathogenetical measures [37,38]. It is remarkable that the criteria selection processes did not implement a reference to *causality* - and also a discussion if the different criteria originate from, or adhere to, a dominant cause or if the disparate criteria appear from disparate causes. These problems have a direct impact on the discussion if SLE is a one disease entity or not (see a discussion related to Fig. 1, in paragraphs 1.1.2 and 2.1.2).

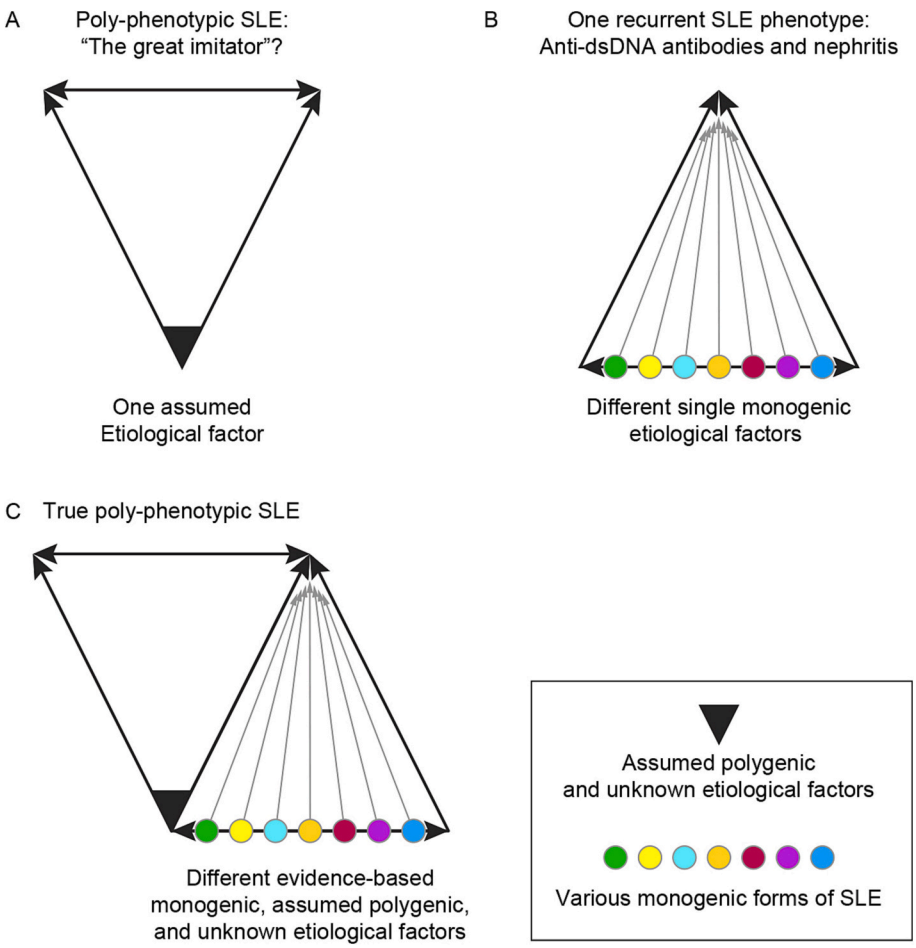

Fig. 1. A problematic discussion aimed to understand if SLE is a poly-etiologic/poly-phenotypic syndrome or "a one disease entity". Concepts that focus on a causality-mediated and consequential network of interdependent pathophysiological events have not been presented or discussed in the evolution of SLE classification criteria. In Fig. 1A, an assumed single causal factor promotes SLE composed of various coherent and incoherent disease measures. If so, SLE is a "one disease entity" and the poly-phenotypic nature of the syndrome is in harmony with the nosological term "great disease imitators", according to fulfillment of the idiom: *One major cause – different clinical phenotypes – one disease.* An opposite interpretation of that illustrated in Fig. 1A derives from observations that different SLE syndromes are individually caused by a specter of gene defects (i.e. monogenic (53;55) and poly-genic (53;58) SLE, Fig. 1B). Although the monogenic defect in each case is singular and unique, most of the patients (and experimental mice) suffer from a dominant and reiterated pauci-symptomatic syndrome, where prevailing symptoms like anti-dsDNA antibodies and nephritis characterize the disorders. Since the cause is monogenic and disparate between patients, SLE is in this context not at all a "one disease entity" (Fig. 1B, the numbers of single mono-gene defects in the figure is for illustration only). What will the pictures tell us if we merge Fig. 1A and B into a Fig. 1C? Then, we get a figure that objectively describes a poly-etiological origin of orderly classified SLE, and SLE as a heterogenous poly-phenotypic syndrome (Fig. 1C). A definitive conclusion that emerge from Figs. 1A-1C is that SLE as classified and diagnosed today, can from theoretical reasons not be regarded as a "one disease entity".

The three procedures discussed above have not been based on testable science-based and concise hypotheses that implement causality in the evolution of classification criteria. Particularly, when statistically probing new classification criteria versions against former versions (as in [32,33,39]), it is only vaguely problematized the fact that the "new criteria" versions inherit many of the criteria that constitute the former criteria versions. This is recently documented and discussed (see e.g. Table 1 in reference [28]). This table demonstrates reiteration of criteria in all versions of classification criteria since 1971 [29–33].

Another main problem relevant to all the published classification criteria versions is the absence of information, and even a discussion, on *what ties the criteria together in SLE*. Do they all belong to a unique and specifically activated pathophysiological network, or do they appear sporadically and incoherent as *"difficult to explain"* phenomena [28]? Central in this discussion is whether *diagnostic criteria* are theoretically and logically possible to establish when we consider current insight that emerge from studies on classification criteria [29–33].

1.3. SLE classification criteria: Do they claim superiority over the possible and theoretically preferred authority of SLE diagnostic criteria?

It is problematic to define SLE diagnostic criteria in light of the attribution rules and composition of classification criteria. This problem relates to the factually incoherent definition(s) of the fundamental etiology(ies) of SLE. Two scenarios provide ideas that may explain how to understand the problematic but possible interactive roles of classification and diagnostic SLE criteria, and how classification criteria may preclude development of diagnostic criteria:

1. The classification criteria are based on phenomenology – represented by an intuitive[3] collection of criteria, while diagnostic criteria are

[3] Intuitive means in this context instinctual selection of disease measures (criteria) based on insightful priorities, but they are not connected with aspects related to a causal etiology, and coherence of the criteria was not an insisted claim.

based on causality – a succession of pathophysiological events instigated by one (or several disparate (?)) basically identifiable cause(s) [1,40,41]. Thus, the SLE classification criteria lack a causality perspective. The spectrum of classification criteria is expected to be larger than the restricted spectrum of putative diagnostic criteria as a consequence of the authoritative and restrictive nature of the causality principle.

2. SLE diagnostic criteria must rely on a factual causality principle that defines the subsequent appearance of diagnostic criteria categories. This is in clear contrast to the vague scientific description of the origins of SLE classification criteria. *A relevant question is if all classification criteria are documented to be inherent parts of an SLE syndrome - or not,* and if they all are inter-related in a common inflammatory network, as should be expected if SLE is "a one disease entity" instigated by a dominant unifying stimulus (see below, and reference [28] for further discussions).

These unsolved problems are based on the perception that we do not know how to define SLE, and more specifically: we do not know how to define the major etiological factor(s) that are inflamed downstream from "identified basic genetical roots" in SLE – whether one major etiology or several disparate; like those appearing downstream in different monogenic and polygenic SLE versions (Fig. 1, and discussions linked to this figure). Importantly, this brings again into the discussion forum if SLE is "a one disease entity" [28] or not. If SLE indeed is "a one disease entity" with one dominant inciting etiology, this hints to SLE as one of the great imitators [42,43] evidently presenting different phenotypes (see Fig. 1 for details). Alternatively, disparate SLE variants that present a multiple of phenotypes may derive from a series of disparate, individually unique etiologies, like monogenic and polygenic SLE variants (Fig. 1).

As discussed before [28], there is no reason to believe that the steadily increasing numbers of etiologically incoherent (?) SLE classification criteria [29–33] will provide us with more pertinent insight into the core process(es) that *promote, maintain, and aggravate SLE*.

SLE classification criteria are, whether we like it or not, used as quasi diagnostic criteria with inadequate scientific justification to serve this purpose. This comprehension defines the theoretical conflict between SLE as an enigmatic disease confused by non-categorical criteria on one side, and an assumed SLE with clear diagnostic markers linked to specific patho-biological processes on the other, in harmony with the causality principle. A conclusion that can be drawn from this discussion is that SLE classification criteria may preclude progress in development of SLE diagnostic criteria systems.

2. SLE as "a one disease entity" – Can the causality principle theoretically support this definition?

If SLE is a disease incited by one dominant cause (in sense of a mono-etiological syndrome), this may be a central argument for SLE as "a one disease entity". There are many arguments supporting this paradigm, as has recently been more precisely discussed in reference [28]. Hucklenbroich has concisely and concretely discussed the term "disease entity" in his study *"Disease Entity as the Key Theoretical Concept of Medicine"* [40]. He states that "*It is the concept of disease entity that is of key importance for understanding medical pathology and theory of disease"*. He brings this connotation further by proclaiming that "disease entity" is a theoretical concept of medical science, and that "disease entity" is not definable by empirical terms like experience or insight, but by evidence (this is further discussed in references [28, 40, 44]).

2.1. Do classification criteria promote SLE as a one disease entity - and are anti-nuclear antibodies (ANA) essential to understand the nature of SLE? Some complex questions and illogicalities

Several central and critical questions relate to classification criteria and their clinical impact:

- What is the scientific basis for the early objective norms and standards that were developed for selection and clinical implementation of classification criteria [29,30]?
- Are they relevant to understand the traditions settled in the selection of criteria and the evolution of subsequent classification criteria versions [31–33]?
- Have e.g. arthritis and nephritis the same values as classification *and* diagnostic criteria, and do they derive from the same identifiable (causality-related) etiology?
- What is the rational for implementing a positive ANA test as mandatory in order to initiate the SLE classification process, when the molecular specificities of ANA are plural, but unexpectedly not a concern [33]?
- How specific for SLE are systemic (organ unspecific) autoantibodies [23,45–50]? For example, antibodies to histones do not have the same SLE diagnostic impact as anti-dsDNA antibodies. However, even anti-dsDNA antibodies cannot by themselves be regarded as unique for SLE (evidentiary arguments for this view are given in [20,23]).
- What are the basic and formal arguments for the idea that the criteria are validated to classify, but not to diagnose SLE?
- One further problem needs critical considerations. According to the 2019 EULAR/ACR SLE classification criteria, patients are excluded from the classification process if the ANA test is negative [33]. That is, a positive ANA test at any timepoint is a mandatory entry criterion. To this, we can conclude that ANA counts irrespective the molecular specificity of the different ANAs, like specificity for histones, non-histone proteins, regulatory and repair proteins, proteins that affect dynamic chromatin structures, transcription factors and RNA/DNA molecules, and irrespective time points for their appearence. That is, ANA is a mandatory entry criterion, even if unlinked in time from clinical symptoms, and molecular specificities of ANA is actively ignored as trivial and insignificant in this context. In contrast, the iconic anti-dsDNA antibodies are not selectively defined as mandatory to initiate the classification process.

Answers to these questions are not provided in the relevant literature on SLE classification criteria, where open-minded critical comments are not part of the discussion.

2.2. Unique etiologies promote poly-phenotypical SLE variants – is this supporting the epitome SLE as "a one disease entity"?

There are clear arguments for and against SLE as a "one disease entity" [51]. These are discussed in the following text, but only superficially discussed in the original literature.

The perception of SLE as an integrated entity is problematic from the following reasons. Arguments forcefully claim SLE as an "entity", despite the fact that SLE cohorts classified by criteria may be poly-phenotypic (see a concise discussion in [28]]. The term "one disease entity" reflects that the syndrome with high probability may evolve in response to one single dominant cause. This is essentially illustrated in Fig. 1A. Here, SLE is a tentative mono-causal disease presenting symptoms that may differ from patient to patient, a fact that implement SLE among the great disease imitators [42,43], similar to characteristics of the mono-causal, but poly-phenotypic disease Covid-19 infection [52]. This is an essential example of the imitation idiom: *"One major etiology – different clinical phenotypes – one disease"*. However, an opposite interpretation of the syndrome illustrated in Fig. 1A derives from observations that different SLE-like syndromes are caused by a spectrum of unique single gene deficiencies (monogenic SLE [53–56]). This model is illustrated in Fig. 1B (for illustrations, 7 fictive examples of monogenic SLE are included). Polygenic SLE [57–59] may fit into the poly-phenotypic SLE model illustrated in Fig. 1A, but data in the literature is not clear (see discussions in [60,61]).

Although the genetic defect in each monogenic SLE is identified as

unique and singular, many of the patients suffer from a dominant and reiterated pauci-symptomatic syndrome, where prevailing core symptoms like anti-dsDNA antibodies and nephritis characterize many of the patients and relevant experimental animals. These genetic conditions are still often denoted *lupus-like* disorders, while SLE provisionally classified by criteria is without hesitation denoted unequivocal SLE (discussed in [28]). Thus, a variety of monogenic/polygenic SLE versions may exhibit both similar and disparate clinical disease patterns [53–56]. Despite this fact, the SLE variants may not at all represent a "one disease entity" as is discussed as follows.

What will the illustration tell us if we merge Fig. 1, panels A and B into a panel C? The principles that appear in the merged Fig. 1C demonstrate that SLE is not representing a "one disease entity", provided that the SLE diagnoses in Fig. 1A and B are used correctly. The phenotypes covered by the term "poly-phenotypic" in Fig. 1C fulfill the authoritative rules to definitively classify the disorders as SLE. This is true irrespective which of the criteria are observed or not: Like positive tests for anti-dsDNA antibodies, nephritis, dermatitis, cerebral lupus, complement consumptions, serositis, arthritis, and other criteria (see e.g. information provided in [54,55,58–61]). These criteria are common denominators for many SLE variants. The indicated common criteria may have developed from a manifold of unique and distinctive etiologies, and may therefore represent "disparate disease entities" or a group of SLE disorders like "genuine SLE" and "SLE-like non-SLE" syndromes (see a discussion in paragraph 4.1.2).

2.3. Do the classification criteria substantiate the causality principle – If then, can they be implemented as an authoritative diagnostic algorithm?

Certain classification criteria execute a clear diagnostic impact as they serve as evidences for a causality principle aspect in SLE. *Causality here means that there is a definable primary etiology that starts an identifiable and predictive chain reaction promoting down-stream interconnected symptoms (or criteria). Hence, they are integrated in a pathophysiological network* (like anti-dsDNA antibodies, exposure of chromatin fragments, nephritis, and complement consumption as illustrated in Fig. 2). That is, an anti-dsDNA antibody in complex with chromatin fragments induce downstream activation of an inflammatory network that reflects classification criteria for SLE (see Fig. 2 for examples). *It is important to comprehend that in this pathophysiological context, it is not anti-dsDNA antibodies that serve as the cause, and not exposed chromatin fragments neither: The formed immune complexes between the antibody and chromatin fragments serve as the cause that incite* e.g. *lupus nephritis and connected downstream inflammatory networks (see a discussion in paragraph 4.1.1).* This example teaches us that a cause may be complex, and may be composed of disparate single molecules that constitute stable (immune) complexes. This dynamic network is closely linked to SLE, and many scientists will define such complexes as evidences for SLE (discussed in [12]). If they are unique for SLE remains an yet unresolved problem.

Criteria-based SLE cohorts represent standards by which putative SLE diagnostic criteria should be probed against. This is problematic, since patients enrolled in SLE cohorts are poly-phenotypical, as they are characterized by binary disease measures, like, for example, with or without anti-dsDNA antibodies, with or without lupus dermatitis and lupus nephritis, or with or without complement consumption. In fact, SLE cohorts cannot be validated for basic studies of diagnostic criteria due to the clinically heterogenic poly-phenotypic nature of the SLE cohorts. This heterogeneity is real irrespective whether SLE is truly poly-etiologic, or due to the imitating nature of SLE as "a one disease entity". This raises the principle problem that operational limitation of the classification criteria lacks a strategic definition and an interconnected coherence.

In an antique narrative,[4] "Lupus" was described as a serious skin disease [62–64]. This may be interpreted as a combination of nephritis (invisible but serious) and dermatitis (visible skin disease). This is fair to assume since current science describe both lupus nephritis [34,65,66] and lupus dermatitis [67–69] as manifestations instigated by anti-dsDNA and anti-chromatin antibodies interacting in situ with exposed chromatin fragments [34,67–70].

Why not attach to this simplified version of SLE and accordingly create cohorts based on few central criteria that may adhere to the causality principle, and probe them against the whole spectrum of classification criteria. By this, we can analyse if anti-dsDNA antibody-induced nephritis and dermatitis promote the whole spectrum of (interconnected) classification criteria, or eventually if a more restricted group of them appear as downstream criteria. Such recurrently appearing criteria may indicate that they are involved as result of a causal dependency. Other classification criteria that are not detected as obligate in such homogeneous SLE cohorts are to be regarded as circumstantial indicators and not as "hard" evidences (see paragraph 3.1.1 for a detailed argumentation of forensic terms applied to weight of criteria).

We have to make a principal decision: There is a need to re-define and implement the term "one disease entity" for SLE by attempting to strictly follow the causality principle [71], discussed in [28]).

In other words, we have to redefine SLE to focus on a syndrome emerging from major identifiable and dominant etiological origins (the central etiological origin, in sense of a unified genesis) with consequently activated secondary pathogenic events – the latter can be regarded as downstream criteria. This means that the clinical measures are all confined in a common fate destiny defined by pathophysiological events (discussed in more detail below with a focus on events described in Fig. 2). In this context, contemporary settled criteria like alopecia, arthritis and serositis may be regarded as circumstantial indicators but not as hard evidences for SLE (see paragraph 3.1.1).

3. SLE in light of "the causality principle" – How to incorporate this principle in a diagnostic context

In the literature, and in medical practice, SLE materializes itself full of contrasts and insufficiently explained paradoxes [10,12,72]. Even anti-dsDNA antibodies, which are regarded to be nearby pathognomonic for SLE,[5] are obligate and frequent manifestation in malignancies and in many infections [20,72–77]. Another paradox says that anti-dsDNA antibodies are claimed to promote lupus nephritis by binding exposed chromatin fragments in glomerulus basement membranes and matrices [78–80], while many other studies claim that anti-dsDNA antibodies are nephritogenic because they cross-react with inherent glomerular constituents (discussed in detail in [34,81]). These, and other similar conflicts have been described, but attempts to seriously solve such conflicts by sound, interpretable and conclusive studies are still awaited from groups that publish these contradictory observations. This is a problem, since many incommensurable conflicts have been described, but they are still mostly overlooked or marginalized.

This brings the "causality principle" as a core focus into this discussion. Before we can clearly describe how humoral autoimmunity promotes disease processes in SLE, effects of autoantibodies will remain poorly defined and will represent a factor causing diseases *or* they will remain as pathophysiological epiphenomena.

All real events are results of a cause. This principle declares the existence of a logical relationship between two events, the cause and the

[4] The disorder "lupus" is described as a serious skin disease already in ancient Greece (62–64).

[5] https://en.wikipedia.org/wiki/Anti-dsDNA_antibodies: Anti-dsDNA antibodies are incredibly specific for SLE, with studies quoting nearly 100%, and are therefore used in the diagnosis of SLE.

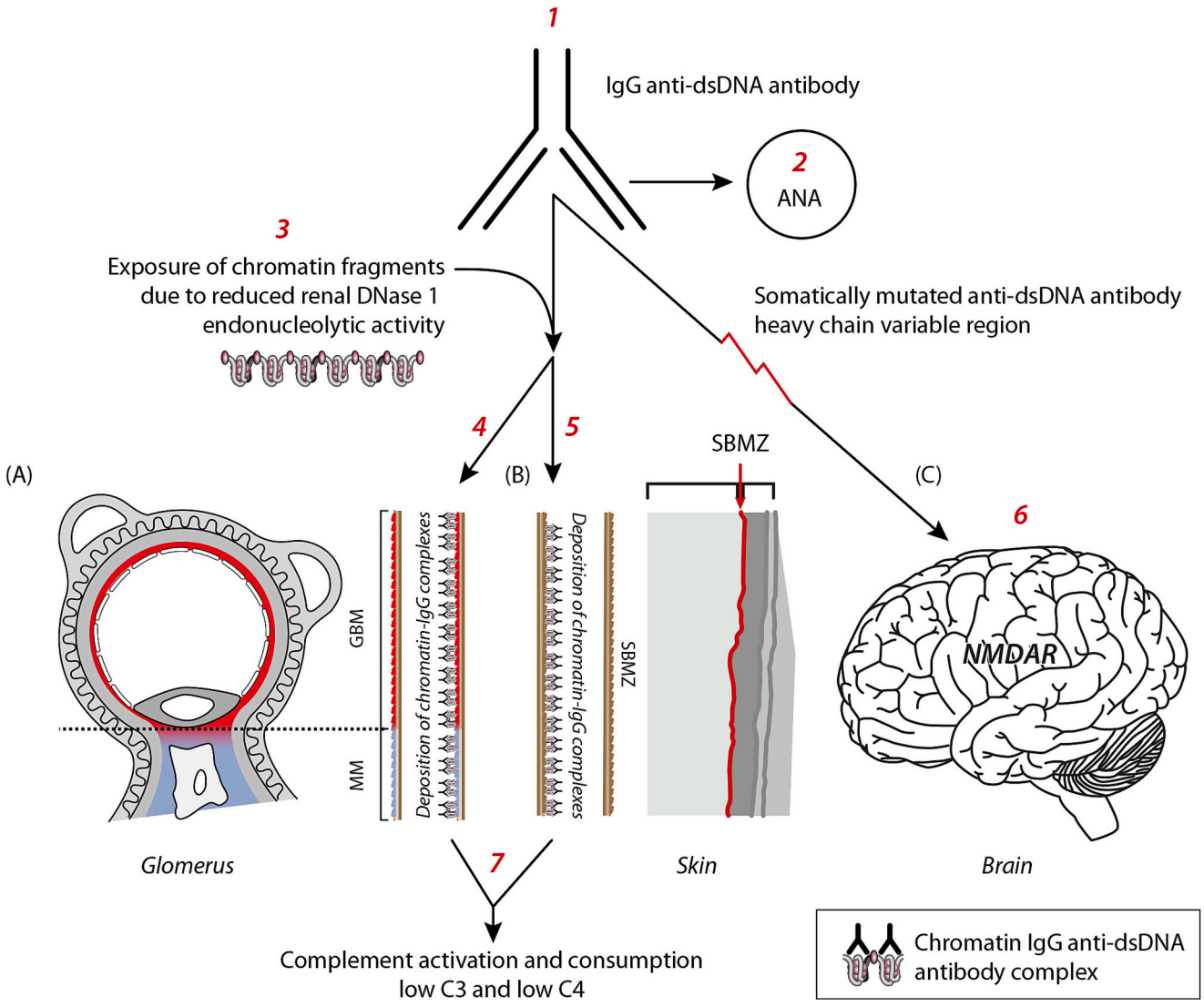

Fig. 2. Identification of an exemplified central and interactive set of criteria to categorize one SLE version as an alternative to classify SLE by classification criteria. The clinical criteria linked to anti-dsDNA antibodies are lupus nephritis (A), lupus dermatitis (B), and cerebral lupus (C). As an inciting factor, termination of tolerance to dsDNA result in affinity-mutated anti-dsDNA antibodies. These antibodies may cause a consequent activation of an interactive network of pathophysiological events that account for the following SLE-associated measures: (1) Anti-dsDNA antibodies, (2) ANA, (3) Exposure of chromatin secondary to silenced renal DNase 1 endonucleolytic activity (see text for details), (4) Lupus nephritis, (5) Lupus dermatitis, (6) Lupus brain disease incited by cross-reaction of somatically mutated anti-dsDNA antibodies with NMDAR, and finally (7) complement activation and consumption – low C3 and low C4. *At least fulfillment of criteria number 1–3 in combination with any of criteria 4–7 is equivalent to a category of SLE diagnosis.* Except for silencing of the renal DNase 1 gene (here criterion #3), all these criteria are, and have been, influential authorities as diagnostic criteria, as they are pathophysiologically involved in SLE. *Criterion #3, exposed chromatin fragments, is a central partner that transform anti-dsDNA antibodies from being a clinical epiphenomenon into a significant pathogenic factor (see text for details)*. Thus, the 7 criteria are interrelated basically due to termination of tolerance to dsDNA (and to exposure of chromatin constituents). This is a sine qua non for appearance of the criteria listed in the figure: They are interdependent and interactive and serve as cardinal symptoms in SLE. This is an exemplified "full" picture of one category (or one version as a "one disease entity") of SLE.

effect, and an order between them: *the cause always precedes the effect*. This statement is in clear conflict with the SLE classification criteria, which are accepted whether interdependent or not, and whether appearing timely independent from each other or not. Their mutual, cooperative and consequent succession has not been discussed in the relevant literature. Rather, according to the authoritative rules, criteria may appear at any time point without restrain (see the original literature [29–33]). No causality is considered or discussed in the authoritative rules formulated in the dominant SLE classification criteria versions [29–33]. We may as a consequence of this perception conclude that the SLE classification criteria are not implemented in the causality principle and *they do not represent a reflection of one unifying cause*: They are equivocal diagnostic criteria (see statements in the Introduction).

3.1. SLE criteria in light of forensic science terminology – the impact of the terms "guilty or suspected" in sense of criteria as "hard evidence" or "circumstantial evidence" for definition of SLE

We face a central problem: We need to determine the basic etiological factor(s) in SLE, and separate these tentative causative factors from circumstantial indicators. The causality principle tells us that every disease measure, and the disease itself, has a cause that is unique and identifiable. This simple statement has a forensic science connotation: To search for, and to define, relative weights of evidences as in a criminal case: Both "hard" evidences and "circumstantial" evidences (indicators) evolve from concrete events (a crime act, or in analogy to the SLE problem: a pathophysiological process, see thoughtful

discussions in [82–84]).

In a forensic investigation, the "hard evidences" describe, and reflect, the origin and factual existence of the causal factor. The "circumstantial evidences (or indicators), in a wider framework, represent measures that are less stringent, indirect, and may open for interpretations and alternative explanations (see a systematic discussion in [85]). Principally, however, circumstantial indicators may allow investigators to *assume* that a real event has occurred due to a willed yet hypothetical act.

As in forensic science, medical science intends to explain the character and origin of a vital clinical problem - like understanding the natural cause of SLE. This is vital for development of causal therapies. It is therefore an imperative to describe the pathophysiological processes that *account* for the syndrome. The clinical consequences of an SLE-promoting etiology are materialized into two traits: "hard evidences", and "circumstantial indicators" that in sum may describe the etiological origin of a pathophysiological process. *The indicators are not proving anything*, but hint to a possible origin of the process(es). This is relevant to say also for certain SLE classification criteria.

3.2. Relevance of the forensic definitions of hard evidences and circumstantial indicators to the SLE classification criteria

Among the SLE classification criteria, some may be objectively and causally linked to a genuine SLE process, but some may be not. The latter means that proof for connotation with a basic cause has not been provided. For example, do alopecia, arthritis or serositis serve as circumstantial indicators or hard evidences pointing at SLE? Noteworthy in this context, can it be that the criteria (as circumstantial indicators) may be misleading both in a forensic [85], and in an SLE classification and diagnostic context. Appropriate speculations around this problem are not provided in the relevant literature on SLE (see e.g. [29–33,71,86,87]).

Circumstantial indications are the fragile elements when we discuss how to comprehend SLE as classified by both demonstrative and indicative classification criteria. This fragility reflects how the classification criteria are formally selected, and how they are incorporated in SLE research by formalized authoritative rules. When we read the relevant literature on SLE classification criteria, it is problematic to observe an absence of penetrating discussions that focus on the individual impact of each criterion, defining its etiology, and whether it is linked to other criteria in an interactive and interdependent pathophysiological network. Another important aspect relates to lack of scientific studies that could explain why all the selected classification criteria *adhere to* SLE – and whether they are etiologically interconnected.

The criteria selection processes do not elucidate the problem how classification criteria are involved in the initial SLE disease process. Some examples may be helpful to understand this dilemma. In a recent study [88] it is stated that "*Hemolytic anemia, proteinuria, lymphadenopathy and anti-Sm antibodies were predictive only of pericarditis, whereas pulmonary fibrosis and GI infarction were predictive only of pleurisy. Both pericarditis and pleurisy are covered by the term serositis* [89]. *This means that pleurisy and pericarditis represent examples of serositis with (individually) unique etiologies. Fever, Raynaud's syndrome, and anti-DNA antibodies were predictors for both pericarditis and pleurisy*". In another study [90], oral ulcers are demonstrated to correlate negatively with "seropositivity" (low complement, high levels of anti-dsDNA antibodies). No information on etiologies of these measures is presented, and no explanation on how we should understand the patho-biological aspects of this information. Likewise, it is difficult to assess from the literature concise information that describes the basic etiology of alopecia or arthritis/arthralgia in SLE, which are accepted and validated as SLE classification criteria.

From this, it may be fair to conclude that for some criteria, it is not possible to categorize them either as "hard" evidences, or circumstantial indicators. Criteria as those described in Fig. 2, anti-dsDNA antibodies, exposure of chromatin fragments, nephritis, dermatitis and cerebral lupus, reflect a factual causality principle that predict and rationalize why the criteria exists in response to an initial (genetically determined (?)) regulatory defect. This implies that the combined appearance of anti-dsDNA antibodies, silencing of the renal endonuclease DNase 1 and a consequent accumulation of extracellular undigested chromatin fragments in glomeruli, form the basis for immune complex mediated lupus nephritis combined with anti-dsDNA antibody-associated lupus dermatitis and cross-reactive anti-dsDNA antibodies with cerebral lupus (is this process compatible with genuine SLE (?)) This is discussed in detail in [34], and details are given in paragraph 4.1.1, and discussed in Fig. 2). The combination of anti-dsDNA antibodies and loss of renal DNase 1 may therefore be regarded as central diagnostic criteria (in analogy to "hard evidences) for SLE. This is possibly at difference to the pathophysiological pathways resulting in e.g. serositis, arthritis or alopecia.

4. A central set of SLE criteria - an example of "hard" evidences in search for SLE diagnostic criteria

The following version of the SLE syndrome is based on impact of anti-dsDNA/anti-chromatin antibodies and – importantly – a concomitant extracellular exposure of chromatin fragments in glomeruli due to loss of the renal DNase 1 endonuclease activity (see below). The combination of these two factors promotes a consequent progression of anti-dsDNA antibody-mediated nephritis [34], dermatitis [67–69] and cerebral affections, the latter most probably due to cross-reactive anti-dsDNA antibodies, independent from exposed chromatin ([10,12,72,91–94], see details in Fig. 2). These proposed diagnostic criteria basically evolve from termination of immunological tolerance to chromatin structures. The ensuing antibody production and exposure of chromatin fragments allow the anti-chromatin antibodies to promote functional pathogenicity. This will impose consequent downstream criteria sufficient to diagnose (one category of) SLE. In this scenario, the causality principle is fulfilled and may explain *why* the criteria appear – very much in contrast to appearance of some classification criteria that probably are not linked to a unified causal etiology, like alopecia, serositis or arthritis.

4.1. Molecular interactions between anti-dsDNA antibodies and chromatin fragments - a defined cause and its downstream criteria clusters that distinguish one of several categories of the SLE syndrome

Anti-dsDNA antibodies, chromatin fragments and possibly neutrophil extracellular traps (NETS) are involved in classical organ affections in SLE [34,50,95–97] like lupus nephritis ([34], Fig. 2A), lupus dermatitis ([67–69], Fig. 2B), and cerebral lupus ([91,92,98], Fig. 2C). As an inciting factor, termination of immunological tolerance to dsDNA results in production of potentially high avidity anti-dsDNA antibodies [19]. These may in complex with chromatin fragments cause a consequent downstream activation of a network of inflammatory events that account for the following SLE-associated criteria (as numbered in Fig. 2): (1) Anti-dsDNA antibodies, (2) ANA (reflecting presence of the anti-dsDNA antibodies and other anti-chromatin antibodies), (3) Exposure of chromatin fragments secondary to acquired inflammatory-mediated silencing of renal DNase 1 endonucleolytic activity (see below), (4) Lupus nephritis, (5) Lupus dermatitis, (6) Lupus brain disease. This latter disease manifestation is an exception from the immune-complex models in (4) and (5), and is incited by cross-reaction of somatically mutated anti-dsDNA antibodies with the *N*-methyl-D-aspartate receptor (NMDAR), very much like the reported somatic mutant of an anti-phosphocholine antibody of the T15 idiotype, the U4, that acquired reactivity with dsDNA and a variety of phosphorylated macromolecules [99–102], and finally [7] complement activation and consumption – low C3 and low C4. These criteria are implemented in the 2019 EULAR/ACR recommendations [33], except for criterion 3; loss of DNase 1 enzyme activity. *At least fulfillment of criteria numbers 1–3 in combination with any of criteria 4–7 is sufficient to diagnose an active category of "genuine" SLE.* Except for the silenced renal DNase 1 gene (here criterion 3), all these

measures are, and have been given influential authorities as SLE classification *and* putative diagnostic criteria. They are pathophysiologically involved in evolution of SLE, and thereby they fulfill the causality principle as discussed above.

Criterion 3 needs a particular comment because it has just recently been described as a contributor to progression of lupus nephritis from mesangial into end stage nephritis. This contribution is basically due to a progressive loss of renal DNase 1 enzyme activity during murine and human mesangial nephritis [103–105]. The resultant glomerular exposure of undigested chromatin fragments has been demonstrated to be a central partner that transform anti-dsDNA antibodies from being a pathogenic epiphenomenon into a significant pathogenic factor [34,72,103]. With respect to clinical documentation in a diagnostic working program, low expression of DNase 1 protein and consequent exposure of extracellular chromatin can directly be visualized by co-localization immune electron microscopy in kidney biopsies [106] or indirectly as low levels of the renal endonuclease DNase 1 in urine samples from individuals with progressive lupus nephritis [107].

In this way, the complex and coherent nature of SLE may be explained by concise and explicable pathophysiological network-processes. These processes, as outlined and exemplified in Fig. 2, may serve as "hard evidences" where complexes of anti-chromatin antibodies and chromatin fragments are the executors of the lupus nephritis process. Notably, criteria like alopecia, serositis, or arthritis are not causally involved in this model, and serve in our context only as "circumstantial indicators" for SLE, and not as partners in a causal anti-dsDNA (and anti-chromatin) antibody-mediated inflammatory network. "Circumstantial indicators" may indeed reflect processes in SLE, but they are caused by other processes than those depicted in Fig. 2.

Therefore, anti-dsDNA/anti-chromatin antibodies combined with loss of renal DNase 1 and subsequent exposure of chromatin fragments in glomeruli [34] *should be implemented as both classification and diagnostic criteria for one category of SLE.* These criteria are easy to trace as described [108,109], and deficiency of DNase 1 enzyme activity and DNase 1 protein concentration can be straightforward determined in serial urine samples [107]. Therefore, dynamic deficiency of urinary DNase 1 protein is a potential biomarker for *progressive* (but not for initiation of mesangial) lupus nephritis [103,107], and for SLE where nephritis is a central element.

It is here important to stress that loss of DNase 1 enzyme activity is not equivalent to a monogenic SLE, as the deficient DNase 1 in lupus nephritis is acquired - not inherited - and promoted by renal inflammation linked to early mesangial nephritis [103–105].

Thus, the 7 core criteria described in Fig. 2 are causally and functionally interconnected. They are interdependent and interactive and promote cardinal symptoms in classical SLE. However, Functional silence of the renal DNase 1 gene is today not required to classify SLE or to diagnose SLE.

4.2. Can SLE be categorized into identifiable families (or orders) based on sets of interconnective/interactive criteria (or symptoms)?

One way to go further to understand SLE and the impact of classification criteria, could be to redefine the syndrome SLE and split SLE into categories. As an intriguing approach, we could analyse the consequence of constructing a symbiosis of the causality principle and Pisetsky et al.ś important idea to categorize SLE into (homogenous) sub-groups [8].

In this context, it is relevant to consider Isenberg et al.ś highly relevant and thought-provoking description of 988 SLE patient. According to clinical characterization, they were able to categorize patients into 8 dominant phenotypic groups [7]. They state: "*Case histories were carefully reviewed and assigned into 1 of 8 clinical groups: musculoskeletal and/or skin disease only, joint and/or skin and renal disease, mainly serositis, mainly renal, mainly gastrointestinal, mainly central nervous system, joints and/or skin plus serositis, and other, which included predominantly hematologic and/or constitutional or other combinations*". These results, in the present author's opinion, may indicate at least 8 different SLE versions that may be understood as an argument against SLE as a "one disease entity" [7].

A naïve question in this context: The 8 categorized groups of SLE patients point at disparate clinical phenotypes; do these groups of patients emerge by different etiologies or by one dominant etiology? If these patients developed SLE due to one dominant etiology, the enrolled patients could theoretically belong to the epitome "*one etiology-disparate phenotypes-one disease entity*" paradigm. If they arise from different etiologies, the 8 groups may *also* comprise "SLE-like non-SLE syndromes". *The 8 SLE groups are nevertheless, according to Isenberg* et al.*ś description, distinctively distinguishable from each other* (for details see reference [7]). Pisetsky's idea to categorize SLE patients, and Isenberg et al.ś reported observations allowing them to separate SLE patients into groups although the patients are all classified by the SLE classification criteria attribution rules, harmonize with ideas presented in this study.

4.3. SLE diagnostic criteria – Do we have sufficient insight to dismantle the dogma saying that "SLE diagnostic criteria" cannot apply to clinical practice?

Because we are so engaged in this vicious syndrome SLE for so many years, the time has come where we could try to implicate the characteristics of SLE into concise and delimited categories. This would be very much like the idea suggested by Pisetsky et al. [8], and observations by Isenberg et al. [7] when they discuss possibly unique distinguishable SLE groups. This approach may lead us into theories relevant to transform SLE into a rational categorized syndromes and to develop authoritative sets of SLE diagnostic criteria – not for SLE as a comprehensive syndrome, but relevant for individual categories of SLE. For example, in an endless number of published SLE studies, SLE is described as a prototype autoimmune syndrome where autoantibodies against dsDNA are the archetypical criterion and pathogenic factor, and in practice have the position as a diagnostic marker (see discussions in [20,26,110]. One thoughtful question: Is SLE with and without anti-dsDNA antibodies, with and without nephritis, dermatitis and cerebral lupus characteristic of SLE instigated by one dominant etiology? Furthermore, should polyphenotypical SLE without further distinction be enrolled into one comprehensive SLE cohort at all if the aims are to investigate genetics, etiology, and inflammatory networks based on definable causalities. Is it time to dismantle the central role of classification criteria when we aim to classify and diagnose SLE for the purpose of studying central and unifying aspects of homogenous categories of SLE, rather than cohorts consisting of both "genuine SLE" and "SLE-like non-SLE".

5. SLE described as in an ideal world: Each category of SLE develops by one etiology that predicts reiterated identical criteria – is that something to strive for?

Interconnected and interactive pathophysiological processes may evolve as a consequence of one basic cause, and may form the epitome of an understandable syndrome. Provided the etiology is unique and solitary, the ensuing symptoms/criteria are ideally predictable, recognizable and reiterated, and explicable in the patient. This means that the cause predicts sets of interactive criteria (as symptoms or effects) that can be utilized as finger-pointing diagnostic criteria. In this scenario, the cause is the unique and etiological factor, and the downstream interconnected and interactive criteria (as biologically activated parameters like complement activation, and other inflammatory parameters) reflect the unique cause. These are not specifically reflecting the cause since they are common to different incited patho-biological processes. Furthermore, in a reverse situation, criteria may reflect expression of a cause.

In this scenario, classification criteria versions are principally redundant because they embrace criteria that are not connected to one, but probably a pluritum of disparate causes. Therefore, the current SLE classification criteria may promote a complex syndrom that involve both

"genuine SLE" and "SLE-like non-SLE" (SLE imitating) versions (as discussed above). This may result in poly-etiological and poly-phenotypical SLE cohorts.

In an ideal situation we could search for an *interconnected network of pathophysiological processes to diagnose SLE*, rather than factually diagnosing a combination of SLE and SLE-like imitations (see a discussion of this above). Here, we see the contour of a diagnostic archetype; i.e. *a diagnostic primary inciting factor bearing the impact of a basic cause that predict appearance of downstream interconnected diagnostic criteria in sense of inflammatory processes and organ affection – like a downstream falling of domino bricks incited by the first falling brick - the cause.*

We are, however, not living and operating in an ideal world where we can explain the fundamental parameters that constitute an easy-to-define SLE syndrome entity. The discussion presented in this study may nevertheless promote ideas and productive and testable hypotheses that may increase our insight into the nature of the enigmatic syndrome SLE.

6. Concluding remarks - The causality principle in SLE

Research activities aimed to describe SLE are largely separated into two scientific domains: One clinical, mostly a phenomenological and statistical segment, and another mostly basic research applied to concrete effect of genes, of single pathophysiological systems like function of the immune system, of DNA structures and their biological functions, immunogenicity, tolerance, and pathophysiology. The first segment often deals with studies of SLE cohorts established by selected SLE classification criteria. The other segment is connected with the causality principle in biology – causes and their effects. Thus, SLE research is separated into a phenomenological category, and in a causally defined category.

The following conclusions define this study:

- The role of "The causality principle" is largely ignored in development of SLE classification criteria. Time has come to implement this important aspect in forthcoming SLE studies.
- Classification criteria generated over 50 years are contextually similar, and central criteria are reiterated, but they are not causally *interrelated*.
- Classification criteria are today operational as quasi diagnostic criteria.
- This study defines the theoretical conflict between SLE as an enigmatic disease classified by incoherent criteria that provide us SLE cohorts that may at the same time consist of "SLE-like non-SLE" and "genuine SLE" syndromes. The latter version is classified by criteria that reflect "The causality principle". These criteria may serve as diagnostic markers that reflect the cause for their appearance.

The main conclusion of this study is that the (still) enigmatic syndrome SLE cannot be defined as "a one disease entity", but can be transformed into an object for critical scientific investigations based on insightful and critically considered hypotheses – and on implementation of the canonical "causality principle" as a basic research principle. After all these years, SLE is still an enigmatic syndrome – and we still do not know the clinical impact of the many autoantibodies observed in SLE [111]

Disclosure of AI and AI-assisted technologies

The author discloses the use of AI and AI-assisted technologies in the research process and during writing this manuscript.

Declaration of Competing Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author declares that the manuscript is not submitted to other journals, and is not under consideration elsewhere. OPR is the sole author and is fully responsible for content, writing the manuscript, and for decision to submit for publication.

Data availability

The data that has been used is confidential.

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