A Hormone-Based Characterization and Taxonomy of Stress: Possible Usefulness in Managment

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"Stress" is being increasingly implicated in the pathogenesis of a variety of psychological and somatic disturbances. Because responses to stress can vary widely, the absence of a suitable, pathophysiologically based taxonomy of stress responses has hindered physicians in their efforts to devise treatments tailored to deal with specific stress-related problems. It is proposed herein that classical endocrinologic criteria be employed to characterize stress responses in terms of the associated hormonal secretion ratios and their temporal evolution. Ratios of the responses to stressors of the sympathoadrenal system (SA) and the hypothalamo-pituitary-adrenal (HPA) axis can be either unity (ratio = 1) or dissociated in varying degree, with SA or HPA dominance and for more or less prolonged periods. Published reports of studies in both laboratory animals and patients with stress-associated illnesses (eg, post-traumatic stress disorder [PTSD]) suggest that such hormone-secretion ratios together with their temporal patterns can be used to characterize the particular stress response under examination, thereby providing strong support for further study of the proposed taxonomy. Such a classification of responses to stress stimuli will make it possible to test the overall concept by establishing a correspondence between the suggested hormonal profile and the associated clinical/psychological picture, as well as enable assessment of the benefit of a therapeutic strategy designed to fit the particular category of stress response exhibited by the patient.

SINCE 1936, when Selye first described the "general adaptation syndrome,"[1] the rubric of stress has been applied with increasing frequency (often indiscriminately) to an array of clinical situations extending from a large number of somatic illnesses to an even larger number of psychiatric disorders. The criteria used to categorize a particular dysphoric state as a clinical manifestation of stress range from precise to vague. The pathophysiologic events most generally accepted as underlying the stress syndrome include activation of the hypothalamo-pituitary-adrenal (HPA) axis and/or the sympathoadrenal (SA) system.[2,3] Henry[4] and others[5] have emphasized that these 2 systems are not always activated in the same way and that the type of activation may depend on the nature of the stress, as well as on the subject's make-up.

In view of all the attention given to the neuroendocrinology of stress, it is surprising that the balance of these 2 activations (of the HPA axis and the SA system) together with its temporal profile has yet to be exploited in establishing a workable typology of stressors and stress responses. Mason et al[5] have proposed that the SA/HPA ratio could serve as a biological marker for post-traumatic stress disorder (PTSD); however, these authors do not appear to have considered the potential value of using this same ratio, together with the pattern of its evolution, in the development of an inclusive taxonomy of stress-related disorders—one that could be used to improve, if not to establish, clinical management of these disorders.

Other hormones have also been shown to change more or less predictably in response to a particular type of stress. They include arginine vasopressein (AVP), prolactin or other reproductive hormones, and leptin, as well as many additional circulating factors that can be measured in plasma or urine.[3] Still other measurable parameters have been shown to accompany different kinds of stress. They range from various endocrine, peptidergic, monoaminergic, and other neurochemical (particularly 5-HT) changes, to genotypic, electrophysiological, behavioral, or sleep/wakefulness patterns that can be only be revealed by techniques that are either impractical or impossible to use in everyday clinical practice. Examples include 24-hour somnography, brain microdialysis, quantitative morphology of brain areas and in situ hybridization.

Techniques of this nature—although useful in clinical investigation—are of little interest to practicing physicians who currently have no access to relevant measurements other than those obtainable on blood or urine samples. Nevertheless, sufficient information might be obtained from blood (and saliva) and urine samples to permit characterization and evaluation of a patient's stress response, followed by a more informed decision about which therapeutic approach to adopt.

Given the current state of knowledge about the subject of stress and its relationship to illness, the physician is often confronted by a difficult choice: should a given "stress syndrome" be treated, or not? Is there a "type of stress" that calls for a particular type of therapy? This question acquires an urgent character in clinical practice because it is obvious that some stresses need be treated in conjunction with the illness they accompany. In contrast, certain other stresses can be considered entities requiring independent therapy, regardless of the presence or absence of a stress-related comorbidity.

For the investigator, use of a convenient and generally accepted taxonomy is also important in designing appropriate animal models for the study of corresponding pathological entities and/or before producing appropriate knock-out mutant animal lineages.

A PROPOSED TAXONOMY OF STRESS RESPONSES

In this analysis, an attempt will be made to distinguish the various types of stress on the basis of their humoral patterns and the short- and long-term evolution of those patterns. Once these types have been characterized, I shall propose their tax-

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onomy. In clinical practice, taxonomy is the first step in the process of attempting to correlate a form of stress with a clinical syndrome (or with an experimental model). Once such a correlation has been made, the foundation is laid for identifying the most suitable treatment.

Characterization of a stress should be based on diagnostic measurements that are currently available (or can be made readily available) in clinical practice. These parameters should provide information about the relative activation of both the HPA axis (as disclosed by the release of corticotropin [ACTH] and cortisol), and the SA system (as reflected by plasma and/or urinary catecholamines). Since these hormones are typically released in intermittent pulses or in a circadian fluctuation, it would be preferable to use 12-hour or 24-hour urine collections rather than instantaneous plasma or saliva assays of these hormones and/or their metabolites.[6]

These parameters make it possible to determine the ratio of activation of the 2 axes, which can be either unity (ratio = 1) or dissociated (ratio different from 1) and in favor of either the SA (SA ↑) or the HPA (HPA ↑) system. For a better graphic representation it will be shown below that the SA-HPA *difference* (rather than SA/HPA *ratio*) can be used advantageously in expressing the relative activation of these 2 systems.

The other parameter that has to be taken into account in order to characterize a stress and establish its taxonomic place is the *temporal pattern* of changes in successive SA/HPA ratios (or differences) along an abscissa. The time intervals of interest following the onset of stress are: 120 minutes, 24 hours, 7 days, more than 1 week, or (in some chronic cases) months after the onset of the stress. In effect, both the pattern and the duration of the endocrine response depend on the type of stress and the make-up of the subject. The duration of the initiating stress (brief or prolonged) is also an important consideration.

Obviously, the diagnostic value of the SA/HPA ratio will vary depending on whether it is measured during the first hour after exposure to a stressor or several weeks after such exposure. For example, long-term stress-induced activation of the HPA axis (hypercortisolism) has been reported to have detrimental effects in several human disorders, including obesity, dementia, depression, and, perhaps, Alzheimer's disease.[7,8] As McEwen[9] points out, the early response to acute stress is protective of the body. In contrast, prolonged, sustained, or repetitive stress becomes pathogenic, giving rise to, or aggravating such conditions as atherosclerosis, hypertension and the insulin-resistance dyslipidemia syndrome.[3]

For these reasons, it is proposed that, instead of a 3-dimensional representation over time, a bidimensional representation be employed (Fig 1). It consists of a succession of 4 time-related ("very short" for 1 to 120 minutes, "short" for 2 to 24 hours, "long" for 1 to 7 days, and "very long" for 1 or more weeks or months) levels of activation of both the SA and HPA systems. [Note that for the sake of graphic representation the curve shown in Fig 1 must include 1 pre-stress value set by convention as physiologic (see below)]. In parallel to the representation of the above levels of the 2 axes there is the curve that shows the *difference* (or absence of difference) of activation of these 2 systems, with either the SA ↑ or the HPA ↑ . Thus, the upper curve shows the absolute levels of activation of the SA and HPA axes and, more importantly, the lower curve

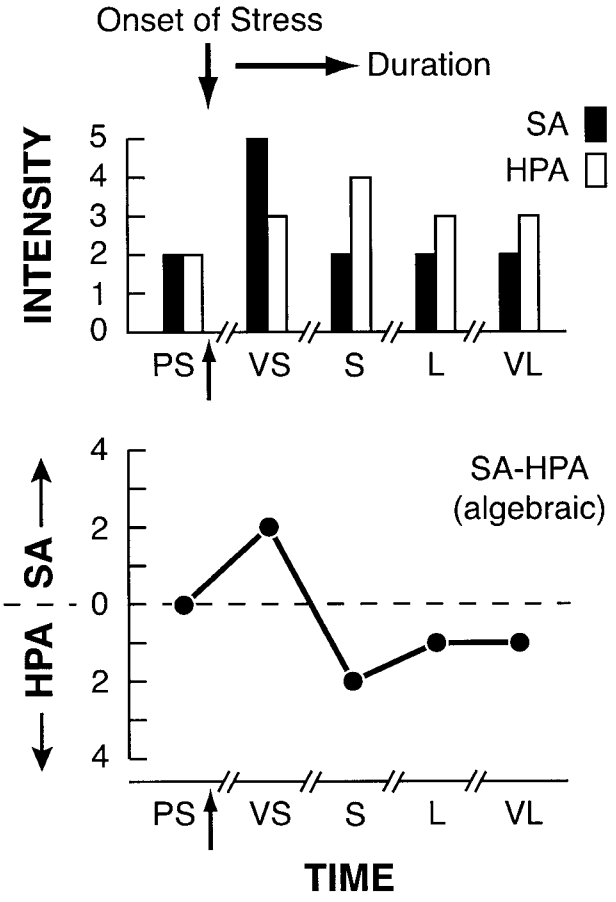

Fig 1. Representation of levels of hormonal activation of the sympathoadrenal (SA) and hypothalamo-pituitary-adrenal (HPA) systems (top) and their relative activation (bottom) as SA-HPA differences at 4 critical time intervals following either a brief or a more prolonged stress. (Y-axis) Time latencies are: very short (VS) = 1 to 120 minutes; short (S) = 2 to 24 hours; long (L) = 1 to 7 days, very long (VL) = > 1 week. The values that follow exposure to stress are preceded by pre-stress (PS) levels, considered (by definition) to lie within the physiologic range. (X-axis) Estimated levels of response: 1 = reduced (below physiological range); 2 = physiological (normal); 3 = moderate; 4 = high; and 5 = very high. The data are taken from a typical case of dissociated response, with SA ↑ in the short term, and HPA ↑ subsequently.

shows the profile of the corresponding SA-HPA differences that characterize the taxonomic position of the stress in question. As shown in Fig 1, when the SA and HPA responses are dissociated, the respective differences are expressed in positive numbers whether the SA is higher (SA ↑) or lower than HPA (HPA ↑). For this taxonomy the *difference* rather than the *ratio* of activation is to be preferred because the ratio flattens the profile of the curve and makes it less apt to express the relative activation of the two systems it is meant to illustrate.

The intensities of the activations are classified into 5 levels: very high (5), high (4), and moderate (3), with level (2) corresponding to quasi-physiological, or basal values. Level 1 is reserved for reduced values (below normal), since stress-bound hormonal decreases have been described in some instances.[3] Note that to express the magnitude of activation of the HPA

and SA axes, it would be logical to determine the range of values, in whatever units (eg, milligrams or picograms, etc) are deemed suitable, corresponding to each of the proposed 5 levels of intensity. But, an attempt by the author to average the heteroclite values reported in the literature for the range of each of the different hormones of interest, gave rise to results that turned out to be more confusing than accurate. For this reason, it was thought preferable to use the 1-to-5 classification in the present taxonomy and to shift the responsibility for placing the data into one of these categories to the clinician or to the experimenter working on stress models.

For the sake of expressing all the differences encountered in pathologic states, decreased levels below the physiological one cannot be expressed as negative values. This is why the below-basal levels are indicated using the level 1 in the intensity range on the X-axis. Note that, by itself, *intensity* is not a quality that can serve as a basis for devising a typology; rather, it is used to calculate the differences from which a typology can be formulated (Table 1 and Fig. 1).

Thus, whatever the intensities involved, the *typology* of a stress will derive from clusters of characteristics that result from SA-HPA differences, together with the temporal patterns of those differences. From such a representation the relative activation of the SA and HPA systems acquires a profile, either of a straight line and at the 0 level (whenever the activations are even) or of a broken line away from the 0 level whenever the activation is dissociated, with either HPA (HPA ↑) or SA (SA ↑) dominance (as in the example shown in Fig 1). Each of the differences, SA-HPA, can reach 4 levels of dominance (ie, 4, 3, 2, and 1), with level 0 of difference corresponding to a parallel response of both systems. Note that level 0 would have been level 1 if *ratios* rather than *differences* were chosen to represent the relative activations of the 2 systems. Such a curve of the differences suffices to characterize a stress and to locate it (even visually as a particular pattern) in its specific position on the taxonomic chart. Also, depending on the availability of data, each point may represent the concentration of 1 hormone per axis (eg, epinephrine [E] and cortisol) expressed within the corresponding period, or the average of 2 or several hormones of the same system, or their metabolites—whenever the laboratory values are available. This way of quantifying the response of each of the 2 axes justifies, once more, the expression of intensity in the above conventional 5 levels rather than in classic units (milligrams or micrograms per milliliter) of concentration.

Table 1. SA-HPA Hormonal Differences at Critical Time Intervals Following an Initiating Stress

	Very Short (1 to 120 min)	Short (2 to 24 h)	Long (1 to 7 d)	Very Long (≥1 wk)
SA - HPA = 0				
SA > HPA or SA ↑				
HPA > SA or HPA ↑				

NOTE. The various values are presented as components of characteristic clusters; however, they can be visualized better by means of the curves of the same data shown in Fig 1.

Abbreviations: SA, sympathoadrenal; HPA, hypothalamo-pituitary-adrenal

In certain situations, if the humoral response is suspected to be oscillatory, repetitive measurement of the differences can be made over time, instead of limiting them to 4 discrete samplings. Of course, if the goal is to make a taxonomy-bound diagnosis and initiate the corresponding treatment at an early stage of the stress response, it will obviously be impossible to take the longer-term responses to stress into account.

The elements that permit characterization of the response to a stress and identification of its location in the stress taxonomy would seem to be as follows:

Characterization of intensity. Level 1 = reduced (below normal); level 2 = physiological (normal); level 3 = moderate; level 4 = high; and level 5 = very high.

Temporal characterization. Prestress value: "basal" (this value is assumed to be physiological, ie, SA = 2, HPA = 2, and SA-HPA= 0); then, 4 post-stress points: "very short" (up to 120 minutes), "short" (from 2 to 48 hours), "long" (from 2 to 7 days), and "very long" (from several weeks to some number of months).

Profile of the differences. The various points of this curve represent SA-HPA differences. They may give rise to a straight line along the 0 level on the Y-axis when, at each point of the abscissa, the levels of activation of SA are of same intensity as those of HPA (as in the case of the classical Selyan-type response). In this case the response is "even." They may well result in a broken line more or less away of the 0 level, when one or more time-points correspond to values of SA different from HPA, with either the SA ↑ or the HPA ↑, or alternating up and down, as in the example shown in Fig 1. In this case the response is "dissociated." These data may be collected using the format shown in Table 1.

As indicated above, and as will be illustrated below, this representation reveals several clusters that may characterize the entities of the proposed taxonomy. For example, the response to a small surgical operation may be classified as "even and short" (and, of course, more or less strong) but the intensity does not constitute a criterion for our classification. Another example (the one shown in Fig 1) is taken from a female patient referred to my neurosurgery division following an unfortunate intramuscular gluteal injection of an antibiotic too close to the sciatic nerve. This procedure immediately induced a dramatic pain lasting 36 hours, followed by a serious depression. (It should be noted that there was no previous psychiatric history). That profile was "dissociated, SA ↑ in the very short time-point, and dissociated HPA ↑ in the subsequent (short, long, and very long) time points. Or, in case of a Selyan "eustress,"[1] one would expect to find a response of moderate or high intensity, and classified as: even, SA-HPA differences close to 0, and long response. In contrast, a Selyan "distress"[1] would be expected to result in a moderate or high-intensity response and characterized as: dissociated, with a HPA-SA difference of 3 or 4 (respectively), and very long.

Additional determination of other relevant hormones (AVP, prolactin, renin-angiotensin, testosterone, leptin and others, or their metabolites) will show response patterns that may help in the classification of a particular type of stress.

DISCUSSION

Selye's "general adaptation syndrome"[1] proposed that animals and humans respond in a more or less uniform, stereotyped fashion to a variety of stressful stimuli. However, as knowledge about the subject advanced, it became increasingly evident that this view of the nature of the stress response was greatly oversimplified. For example, in well-controlled studies of laboratory animals, it has been demonstrated that the nature of the stressor—but, more important, the *way* the stressful experience is perceived by the animal—can determine the pattern of neuroendocrine activation that occurs when the animal is exposed to a particular, investigator-applied stress. Such studies have shown that, as the experimental paradigm is varied, significantly different patterns of neuroendocrine activation may occur including, for example, an appreciable change in the ratio of catecholamine to corticoid secretion.[4,5]

Many other examples from both human and animal studies illustrate the variability of the SA/HPA ratio and therefore lend support to the concept of the typology proposed herein.

In many instances the response will be "even" with a SA/HPA ratio that occurs in response to a stressful experience that remains at unity (or 0 difference in our scale). In other instances there will be a varying degree of dissociation, with the ratio (or the difference) being shifted toward either a SA (SA ↑) or a HPA (HPA ↑) dominance. In both rats and humans submitted to chronic psychosocial stress of the kind that gives rise to a renin-dependent hypertension, there is concomitant activation of both the HPA and the SA axes.[10-12] Chronic parallel ("even") activation of the HPA and SA systems has also been observed in melancholic depression with concomitant arousal and anxiety, together with inhibited sex and eating behaviors.[13] In all of these cases the typological SA-HPA profile (using the paradigm represented by Fig 1) will show a straight line at 0 level—a pattern characteristic of "even" responses that may differ from each other depending on their duration.

There are further examples of dissociation, both within a ratio and along its temporal dimension. Again, dissociation between HPA and SA responses may be characteristic of the nature of the stress and the response to it. Selye himself noted that eustress is accompanied initially by an increase in catecholamine release, followed by an even response, while distress results in activation of the HPA axis.[14] This kind of dissociation appears to reflect in part the type of stress experienced. According to de Boer et al,[15] for example, the SA system is preferentially activated (SA ↑) when animals are actively responding to the kind of environmental challenge that calls for a "fight-or-flight" mode of behavior. Another example of dominance of the SA system is that found in the kind of central nervous system–mediated long-term activation occurring in the labile hypertensive adolescent children of hypertensive parents.[16]

When a stressor elicits behavior directed toward preserving self or species, there is arousal of the limbic system followed by one of several possible patterns of neuroendocrine response, each of which is peculiar to the particular emotion involved.[17]

The HPA system is preferentially activated (HPA ↑) in situations when subjects experience loss of control and become immobile and passive. Under such conditions, the conservation-withdrawal mode of stress response prevails. In this context, Folkow[18] describes the contrast between the *defense* reaction with its dominant SA activation which contributes (*inter alia*) to development of stress-associated hypertension, and the *defeat* reaction with its dominant HPA response (see also Koolhaus and Bohus[19]). The latter, HPA ↑ state, has been described in humans by Seligman as *learned helplessness*[20] or as a *defeat and depressive condition* accompanied by low sex and maternal drives and associated with increased susceptibility to illness and a tendency to develop glucoregulatory abnormalities and insulin resistance—factors that favor a "Cushingoid" pattern of body fat distribution.[21]

According to Henry et al,[11] response patterns to stress can be divided into 2 broad categories. The first is the *fight-flight* response, which is activated when the organism is threatened in its control of the environment. This reaction pattern mainly involves the SA system, with elevation of noradrenaline (SA ↑), preparing the subject for vigorous physical activity. On the other hand, when there is loss of control and failure to meet expectations, the *defeat* reaction occurs and the HPA axis is activated (HPA ↑), with subsequent long-term elevation of cortisol. Such cases would show a broken line in Fig 1, crossing the 0-level line downwards.

Particular attention should be given to the case of PTSD because of its growing prevalence and its increasing prominence in the scientific and popular literature.[3] PTSD has also been identified in an increasing number of children who have been subjected to severe physical and psychological abuse.[22,23] Although PTSD is often easy to diagnose, this is not invariably the case. Yet, regardless of the clinical picture, this syndrome is usually accompanied by increased activity of the sympathetic nervous system (SA ↑) associated with higher urinary levels of catecholamines (and their breakdown products), contrasting (in adults) with diminished activity of the HPA axis (manifested by lower urinary levels of cortisol and its metabolic products).[3,4,24] In these cases, cortisol often reaches lower than normal levels represented by the intensity 1 in our scheme of characterization and justifying the use of the "reduced" level in our scale.

It has been suggested that, in some cases of PTSD, the concomitant presence of alexithymia (an affective disorder characterized by inability to recognize and express emotions) might help explain the disjunction in this disorder between the response to the initiating trauma of the fight-flight catecholamine system (SA ↑) and that of the HPA system, as expressed in the ratio of urinary 3,methyl-4-hydroxyphenyethylene glycol (MHPG)/cortisol.[25] Because of its special hormonal features (provided they have been assessed properly), PTSD may serve as a useful model in which to demonstrate the potential usefulness of applying the system proposed herein for the diagnosis and classification of stress-related illnesses.

Some dissociations may be accounted for by interactions known to occur between the HPA and the SA axes. Both inhibitory effects of noradrenergic neurons on corticotropin-releasing factor (CRF) release[26] and vice versa[26-28] have been reported. But, whatever their interaction, the SA and HPA axes are capable of being activated independently.[29]

Independent changes also occur *within* such systems as the SA and HPA axes. Thus, it is clear that under various physiological circumstances ratios of interest such as those for epinephrine (E)/norepinephrine (NE), ACTH/cortisol, or cortisol/

dehydroepiandrosterone (DHEA) may become dissociated. Thus, dissociation not only occurs between the 2 major axes, but also between the components of the adrenomedullary-sympathetic system or the HPA axis and their respective cascades—systems that can also be regulated separately and probably independently of each other. For example, under conditions of cold stress, the plasma NE shows a distinct increase while plasma E and cortisol levels remain unchanged.[30] These cases provide one more reason, in the above taxonomy, to have the clinician categorize the level of activation of the SA axis, rather than define levels on the basis of plasma E or cortisol alone.

On the HPA axis side, it appears that, in stressful situations, the balance of mineralocorticoid (M)- and glucocorticoid (G)-mediated actions in the control of homeostasis depends on the chronology and the order of their respective effects. M components activation appears to operate in a proactive mode to prevent stress-induced disturbances, while activation of G components promotes, in a reactive fashion, recovery after stress. Thus, in the proactive phase of a reaction to stress, it is reasonable to infer the presence of a higher level of activation when the mineralocorticoids are elevated, despite the low cortisol levels. The typology would show a "very short" and "short HPA ↑ " profile with special mention of the type, M or G dominance.

An imbalance in the reactivity of mineralocorticoid and glucocorticoid receptors in the central nervous system can contribute to the development of stress-related neuroendocrine disturbances capable of causing brain disorders.[31] However, the existence of such perturbations in receptor activity does not invalidate the usefulness of the taxonomy proposed herein; to the contrary, this approach takes into account the possible existence of disturbances occurring within the receptor component of the stress response and thereby helps to point the clinician in the proper diagnostic direction when the manifestations related to these hormones are disproportionate to the degree of HPA activation.

As indicated above, use of the taxonomy described here acquires enhanced diagnostic power by taking into account the coactivation of other endocrine factors. Obviously, in some cases, other humoral factors, together with stress-hormone ratios and patterns, can be measured so as to better understand and manage unclear pathologic entities associated with stress. For example, testosterone levels increase and catecholamine levels decrease in both animals and humans that exercise dominance over their fellows, whereas changes in the opposite direction are observed in submissive-defeated individuals.[32] In another example, Nixon[33] has shown that different coping methods are associated with different patterns of stress response. As the body mobilizes its forces and arousal intensifies in order to cope with a stress challenge, NE (the "fight hormone") and then E (the "flight hormone")[15] start rising, while testosterone and oxytocin (factors concerned with "species preservation") progressively decrease. Then, when the organism becomes fatigued and (at a rate that depends on the organism) exhaustion supervenes, activity falls and hormones of the HPA axis (corticotropin-releasing hormone, ACTH, and cortisol [associated with a state of helplessness]) rise in concert with a decrease in testosterone. These observations suggest that, in stress-related pathologies where a psychosocial factor is suspected, simultaneous assays of other hormones (such as those representing the gonadal axis) may prove to be of diagnostic value. Complementary assessment of other candidate hormones becomes easier to interpret when they can be examined in relation to a profile of the taxonomy suggested herein.

CONCLUSION

This article proposes a method for developing a taxonomy of stress responses that involves employment of readily obtainable and objective measurements of stress-relevant hormones from both the SA system and the HPA axis at various critical times after the initiating stress. The suggested taxonomy distinguishes discrete clusters and profiles of hormonal patterns that point to common underlying mechanisms and possible nosologic entities related to stress. The goal of this analysis is to stimulate clinical studies designed to correlate clusters and patterns like the ones that make up the present taxonomy with a particular clinical picture, in terms of its type, origin, organ system involvement (cardiovascular, digestive, etc), duration, severity, and prognosis.

Only when these questions have been addressed, will it be possible to establish the usefulness of a given therapy. The proposed taxonomy is just a beginning, but, without a starting point, there can be no journey.

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