

When Three Small Abnormalities Become One Large Disease

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Abstract

Medicine often examines physiological abnormalities one at a time. Anemia is assessed by hemoglobin concentration; impaired perfusion by hemodynamic and vascular indices; excessive water retention by serum sodium and urine chemistry. This division is indispensable for identifying discrete pathology, but it can obscure what happens when several modest constraints converge on the same limiting process. A person with a moderately reduced capacity to carry oxygen may compensate adequately at rest. Another person with imperfect microvascular oxygen extraction may also remain asymptomatic. Yet the combined limitation, especially during increased metabolic demand, could produce a functional deficit larger than either abnormality would predict alone. Similar convergence occurs in disorders of water excretion: dietary solute availability, renal dilution, vasopressin activity, and fluid intake are jointly involved in determining whether extracellular tonicity remains stable. This paper proposes a **convergent-constraint model** of selected complex clinical presentations. It distinguishes mechanistic interaction from the casual accumulation of borderline test results, examines competing explanations, and proposes standards for deciding when interactions are biologically and clinically meaningful. The hypothesis is not that every symptom conceals multiple overlooked deficiencies. It is that several independently insufficient limitations may cross a shared physiological threshold when they operate on the same constrained function.

1. A diagnosis may name one variable while the patient experiences a system

A laboratory reference interval answers a useful but narrow question: where does a measurement fall relative to observations in a reference population? It does not directly answer whether a person's tissues are receiving adequate substrate, maintaining stable ionic gradients, or preserving reserve under stress. Similarly, a person can have several mildly abnormal results without having an illness caused by their interaction. Both truths matter. The most serious version of the systems-medicine argument is neither that isolated measurements are meaningless nor that every borderline value is an undiscovered disease. It is that physiology is conducted by interacting pathways whose total capacity may be determined by the point at which a constraint becomes limiting.

Consider a patient with exertional symptoms. If hemoglobin is modestly reduced, the cardiovascular system may compensate by increasing cardiac output and oxygen extraction. If vascular reactivity or capillary recruitment is modestly limited, surrounding vessels and tissues may still compensate. If demand increases during exertion, however, the patient may approach a threshold where further delivery or extraction is no longer sufficient. In that setting, the clinically important object is not any one laboratory value. It is the **relationship between delivered oxygen, extractable oxygen, cellular demand, and remaining reserve**.

The observation is not a license to attribute fatigue to invisible microvascular disease. Anemia, heart failure, pulmonary illness, deconditioning, autonomic disorders, medication effects, sleep problems, and many other explanations remain relevant. The model instead encourages mechanistic specificity: what shared function is constrained, by which independently established changes, and under what conditions should their interaction become visible?

2. What is meant by a convergent constraint?

Three abnormalities can coexist in at least four different ways. First, they can be **incidental**: a mildly abnormal laboratory value, an unrelated symptom, and a separate dietary exposure can occupy the same chart without causing one another or the patient's condition. Second, they can have a **common cause**: for example, systemic inflammation may simultaneously alter iron handling, appetite, and activity tolerance. Counting these outputs as

three independent causes exaggerates their significance. Third, they can have **additive effects**, with each independently contributing to an outcome. Finally, they can interact in a manner that changes the effect of one factor depending on the others. The fourth possibility is the focus here, but it must not be presumed merely because the patient is complex.

In epidemiology, interaction depends on the measurement scale. The departure from additivity of absolute risks is not identical to interaction on a multiplicative scale, and statistical interaction need not establish direct molecular contact between exposures. VanderWeele and Knol's methodological work is useful precisely because it disciplines the loose word *synergy*. Before claiming an effect exceeds expectation, one must state the expected baseline, the contrast being measured, and the assumptions necessary to interpret it causally.

For physiological systems, an additional possibility is **threshold crossing**. Two inputs may produce smooth, individually modest effects until their combined action crosses a capacity limit. The resulting symptom can seem abrupt even when the underlying changes were gradual. Such behavior is familiar in control systems, but demonstrating it in a patient requires more than a plausible analogy. The threshold should relate to a measurable function, not merely to the onset of distress.

3. Example one: oxygen delivery and oxygen extraction are not the same thing

The Fick principle expresses systemic oxygen consumption in terms of cardiac output and the arterial–venous oxygen-content difference. A simplified relation is:

$$\dot{V}_{O_2} = Q(C_{aO_2} - C_{vO_2})$$

This equation directs attention toward at least three distinct constraints: circulation, arterial oxygen content, and tissue extraction. Hemoglobin contributes substantially to oxygen content, but pulse oximetry measures saturation rather than total oxygen content. Consequently, normal saturation does not exclude anemia-related reduction in arterial oxygen content. Conversely, ample arterial oxygen content cannot guarantee that oxygen is distributed appropriately within capillary networks or used efficiently by cells.

Capillary transit-time heterogeneity provides one mechanistic bridge between the macrocirculation and tissue-level exchange. Blood cells do not spend identical amounts of time in every microvessel. When transit times become markedly heterogeneous, raising total flow may not proportionately improve oxygen extraction, because some blood transits the exchange surface too quickly. Angley and colleagues modeled the consequences of transit-time heterogeneity for cerebral oxygenation. Their work does not establish that subtle flow heterogeneity causes a broad category of chronic unexplained symptoms. It does establish why tissue oxygen availability cannot always be inferred from large-vessel flow alone.

Now consider a hypothetical illustration, not patient data. A person has somewhat less oxygen-carrying capacity than usual, a limited ability to increase effective capillary extraction, and a temporary increase in oxygen demand. Each constraint may be compensated in isolation, yet the combined system may fail to preserve adequate tissue oxygenation during exertion. The prediction is specific: when demand rises, the abnormality should emerge in a physiological measure related to delivery, extraction, perfusion, or function. It should not merely appear as a post hoc explanation for fatigue.

The clinical lesson is not to diagnose capillary dysfunction whenever oxygen saturation is normal. It is to avoid confusing a measure of one compartment with the behavior of the entire exchange system.

4. Example two: hyponatremia as a genuine interaction between water, solute, and hormonal control

Low-solute hyponatremia offers an especially instructive example because the underlying physics is sufficiently well characterized to constrain speculation. Excretion of ingested water depends in part on the number of osmoles the

kidneys must excrete and how dilute the resulting urine can become. If daily osmole excretion becomes unusually low, the maximum amount of water that can be excreted may decline. This can happen despite preserved glomerular filtration and intact renal ability to generate relatively dilute urine.

Water intake is another factor: consuming water at a rate below the kidney's excretory capacity need not lower serum sodium substantially. Vasopressin provides a further control, altering water permeability in the collecting duct. Low solute intake, high fluid exposure, and periods of antidiuretic activity can therefore converge on the same outcome: retention of water relative to exchangeable solute, producing hypotonic hyponatremia.

The relationship is not interchangeable with a vague statement that insufficient electrolytes cause every symptom. Sodium concentration is shaped by water balance as well as sodium and potassium handling. Moreover, vasopressin secretion varies with osmotic and nonosmotic stimuli. Joshi and Chou's discussion of beer potomania highlights the dynamic nature of the syndrome, including heterogeneous urine osmolality observations, rather than reducing every case to a rigid formula.

The instructive counterexample is a person with very low protein and solute intake who also consumes large amounts of hypotonic fluid. A reduction in water-excretory reserve may remain invisible while intake is low, then suddenly matter when intake increases or antidiuretic activity changes. The interaction is physiologically interpretable because all factors act on renal water handling. It cannot be generalized to unrelated symptoms merely because a patient follows a restrictive diet.

Importantly, hyponatremia can be dangerous, and its correction can be dangerous. This paper does not advocate self-directed fluid restriction, salt loading, or correction regimens; those depend on clinical severity, underlying cause, duration, and other risk factors.

5. Example three: the difference between reserve and a resting measurement

A person may remain within acceptable physiological bounds at rest while having little capacity to respond to an added stressor. This is the difference between **present function** and **available reserve**. Reserve is not a single substance or universal index. Cardiovascular reserve, renal concentrating and diluting capacity, metabolic flexibility, immune function, and neuromuscular reserve are different biological properties. Their measurement requires domain-specific methods.

A central intuition of the proposed model is that combined moderate constraints may first become apparent during a challenge. The same patient whose circulating markers appear stable at baseline may show an exaggerated deviation, prolonged recovery time, or impaired task performance after an appropriately measured stressor. Longitudinal research by Pyrkov and colleagues examined age-related recovery dynamics in physiological data, offering a precedent for studying resilience as a temporal process rather than a static category. That research does not validate a universal diagnostic test for reserve.

The distinction matters because it changes what the hypothesis predicts. If reduced reserve is the operative explanation, the system should reveal its limitation in a reproducible way when demand changes. If no relevant disturbance emerges under a suitable test, or if a better explanation accounts for the symptom pattern, the proposed constraint model weakens.

6. Why complexity can mislead the clinician

A richly detailed causal story is not necessarily a correct one. A chart with many borderline laboratory measurements provides nearly unlimited opportunities to construct a narrative after symptoms appear. This is particularly dangerous when measurements are selected after repeated testing, the analyst ignores expected biological variability, or only favorable associations are reported.

Confounding is a second hazard. For example, chronic inflammatory illness might independently produce anemia, fatigue, decreased activity, and changes in vascular reactivity. These findings could be interpreted as multiple independent stressors, when a simpler model involving one underlying disease explains them more coherently. Reverse causation creates another trap: patients may change their diet or hydration because they feel ill, making the new exposure a consequence rather than a cause.

There is also a danger in the opposite direction. Specialists may evaluate each system competently yet fail to recognize a cross-system interaction because no one variable crosses its own treatment threshold. The solution is not to abandon specialties or laboratory reference ranges, but to formulate a causal model that specifies how two or more verified abnormalities would jointly impair a shared function.

A useful rule follows: **never treat a variable as a causal bottleneck solely because it is low-normal, high-normal, or outside a population interval.** Establish that it changes the relevant physiological process at the magnitude observed in the patient.

7. A disciplined framework for testing a convergence explanation

The most credible version of the hypothesis uses a sequence of decisions. First, define the functional deficit in observable terms: exercise intolerance measured during exertion, impaired concentration with documented changes in alertness, or an objective disturbance in water balance. Second, identify the shared physiological task: oxygen transport, water excretion, neural conduction, or another specified process. Third, identify candidate constraints and measure them using appropriate, validated tests, not indiscriminate screening panels.

Fourth, determine whether the proposed factors are genuinely independent, partially overlapping manifestations, or downstream consequences of one disease. Fifth, articulate an expected interaction. An interaction might mean a measurable change in a response curve, a threshold at which function deteriorates, or an alteration in the effect of one variable conditioned on another. Sixth, compare that model against the simplest credible alternatives and against measurement noise.

For population data, joint exposure strata and interaction contrasts can clarify whether effects exceed a stated additive or multiplicative expectation. For longitudinal observations, careful within-person measures may show whether change in one variable precedes and modifies response to another. Neither method substitutes automatically for controlled causal inference. Model complexity should be penalized, predictions pre-specified where possible, and validation sought outside the data that inspired the explanation.

At the bedside, the principle remains more modest: recognize that physiology is interactive, but treat according to established diagnoses and demonstrated patient-specific clinical indications. A systems hypothesis is a guide for interpretation, not an automatic reason to add treatments.

8. What would falsify the stronger version of the claim?

A theory that claims all illnesses emerge from hidden interactions is impossible to disprove and therefore scientifically weak. The claim advanced here is narrower. It applies only when multiple measurable factors converge on a demonstrable limiting function.

The proposed explanation becomes less convincing if the symptoms are entirely accounted for by one independently established disorder, if the supposed constraints do not affect the same relevant pathway, or if changes in them fail to correspond to predicted changes in function. It also weakens when the interaction adds no meaningful predictive information over an appropriately fitted additive or simpler model. A favorable interaction term discovered after testing numerous specifications is not enough; external replication matters.

Most importantly, a clinical response after several simultaneous interventions does not tell us which component mattered. Improvements can result from regression to the mean, nonspecific treatment effects, spontaneous

change, or one effective intervention among several. If a hypothesis requires every improvement to confirm it and every deterioration to be interpreted as transient healing, it has ceased to be a testable explanation.

Conclusion: complexity is only useful when it becomes precise

The appealing idea that “three small abnormalities become one large disease” can be either an empty slogan or a useful physiological proposition. It becomes useful only when the abnormalities are verified, the pathway is shared, the interaction is defined, and the predictions differ from alternative explanations.

Human biology is not organized around laboratory columns. Oxygen delivery, solute excretion, inflammatory resolution, and metabolic adaptation depend on coordinated processes, many of which have reserve at baseline and become limiting only under particular demands. Yet complexity must never become an excuse to invent causes from coincidental findings. The ambition of terrain medicine should be to explain the patient's actual physiology more accurately—not to replace one simplistic story with a more elaborate one.

The strongest hypothesis is therefore conditional: **selected clinical syndromes may reflect the crossing of a shared physiological capacity threshold by several independently modest but mechanistically convergent constraints**. That is a precise question worth investigating, even if the ultimate answer is that such interactions matter only in a subset of cases.

Selected scientific literature

1. Angleys H, Østergaard L, Jespersen SN. The effects of capillary transit time heterogeneity (CTH) on brain oxygenation. *Journal of Cerebral Blood Flow & Metabolism*. 2015;35:806–817. doi:10.1038/jcbfm.2014.254. 2. Joshi R, Chou S-Y. Beer Potomania: A View on the Dynamic Process of Developing Hyponatremia. *Cureus*. 2018;10:e3024. doi:10.7759/cureus.3024. 3. VanderWeele TJ, Knol MJ. A Tutorial on Interaction. *Epidemiologic Methods*. 2014;3:33–72. doi:10.1515/em-2013-0005. 4. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *International Journal of Epidemiology*. 2012;41:514–520. Full text. 5. Pyrkov TV, et al. Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit. *Nature Communications*. 2021;12:2765. doi:10.1038/s41467-021-23014-1.

Editorial disclosure: This is a theoretical synthesis, not an original clinical investigation, diagnostic criterion, or treatment guideline. The cited studies establish particular physiological and methodological facts; none individually validates the complete convergent-constraint model. Rewritten and substantially expanded 16 October 2026 for Absurd Health Institute.