Things That Work, When They Do: *Observations about Balancing Acts, Hypotheses, Coins, Metaphors, and Ecosystems, Including the Human Immune System*

> There beyond the village stands an organ grinder,
> and with numb fingers he grinds as best he can.
>
> Strange old fellow, shall I go with you?
> Will you grind your organ to my singing?
> —*Wilhelm Müller, translated by William Mann*

Who are we? Whence do we come, and whither do we go? The present essay attempts to address these questions, and how they are answered, in the context of history, evolution, economics, and medical practices. This search considers several classes of systems that may be bound tightly or loosely, with definitions that vary according to operational needs and proximity. Particularly investigated is the human immune system. Several universal metaphors are noted; of particular importance are those of homeostasis, depth perception, balance, many doors and paths, uncertainty, and the transitory nature of being at home in the universe.

War and Peace

There is a famous story, dating to Pope Innocent III's 13th century war against the Cathars of Languedoc. This is often referred to as the Albigensian Crusade. As the holy armies, under Arnaud Amaury, the Abbot of Cîteaux, closed in on Béziers, the townspeople of all stripes, reportedly some 20,000 in all, took refuge in the Cathedral. A commander is said to have thrown up his hands, asking the future Archbishop of Narbonne how to tell the believers from the heretics. The response: "*Caedite eos. Novit enim Dominus qui sunt eius.*" ("Kill them all. God will know his own.")

This policy of genocide worked, sort of, until it didn't: It gave the Church a couple hundred years of remission, of largely unchallenged hegemony—until the Enlightenment brought about a relapse, followed closely by the Reformation. The issue was that Catharism, along with other gnostic philosophies, had become an alternate, rival repository of cultural knowledge and narratives. This was to be recapitulated in the Enlightenment and Renaissance: Is God to be the seeker or the sought? The revealer or the revealed? Axiom or working hypothesis? Convergence or divergence?

Without delving into modern history and its implications (except to note briefly that Arnaud's tactics and even his words persist in today's wars: "Sometimes it is necessary to destroy a village in order to save it"; and, more recently, a T-shirt slogan popular on military bases reads "Kill 'em all and let God sort 'em out"), I suggest that a healthy social culture requires both dogma and heretical opinion, thinking both inside and outside the box, as it were—but in proper balance. Like the two sides of the same coin: That they are discrete facets is apparent only at close range. Backing off reveals complementarity (assuming you rotate the coin, or circle it); a further retreat, tightly-bonded unity—like, come to think

about it, life and death. (An analogous thought experiment: From inside the orchestra, it is possible to pick out fine-grained characteristics of single players, but discerning a balanced, unified orchestration is not so easy. The opposite is true from the audience perspective. Indeed, one's perception, or, rather, *feeling* of dimensionality, is always optimized for a specific proximity. Too much virtual distance evokes a sense of "flatness". This is obviously so with sight and hearing, of course, but also with social, religious, and political relationships, and with knowledge bases.) Further, this appears to me to be a universal metaphor. William James, in *Principles of Psychology*, takes Hume to task for his contention that everything you need to know about the Self comes from perception.

> But Hume, after doing this good piece of introspective work, proceeds to pour out the child in the bath, and to fly to as great an extreme as the substantialist philosophers. As they say, the Self is nothing but Unity, unity abstract and absolute, so Hume says it is nothing but Diversity, diversity abstract and absolute; whereas in truth it is [in] that mixture of unity and diversity [that the Self lies]....

Tailing Late Rabbits

But in this essay I wish to take the issue away from ecclesiastical, military, and philosophical ecosystems, to mainly survey the human body, and especially its immune system (hereafter abbreviated as IS). To be sure, sorting out the the whole complicated business is like chasing the White Rabbit through warrens within warrens. Still, if we mark our trail, and back off now and then to get a wider view, maybe we can make a serviceable map.

Before entering the rabbit hole, one more initial note about balances (I'll return to the subject in a more generalized context, later). In the world of medicine, there seems to be a necessary, yet somewhat uneasy, dichotomy between researchers, whose novel hypotheses and explanations are both salient and rewarded, and clinicians, for whom it is the confirmation of existing paradigms that is of much greater value. In my view both have merit (and, of course, frustrating weaknesses). My personal style might favor, slightly, the research stance; yet I find myself in a decidedly clinical situation. Thus, in some ways, I sympathize with the Pope's conundrum: Conversion may be preferred, but when you don't know how to pull that off, sometimes it *is* necessary to destroy the town in order to save it. At least, it may buy a respite. Consider the Sorcerer's Apprentice in Goethe's parable, who set in motion a process that made life better, at first. But, finding that too much of a good thing can be calamitous, he tried to destroy his creation, which worked, for a spell—or, rather, for lack of one, when the machine reanimated itself with even more vigor. The sorcerer, of course, knew the right craft, the conjuration of regulation, if you will, to bring the situation under control

Life in the Balance: *Bears of Fine Tuning*

"Homeostasis" is another universal metaphor among living creatures (hence the synonymous "life regulation"). It is a guiding mechanism to tune organisms and quasi organic social systems to the sweet spot between too much order and chaos. In science writing, this is often called the Goldilocks principle: not too hot, not too cold, but just right. In fact, all regulatory systems seem to work on this assumption. All organisms exist in meta- as well as

local ecologies; on all levels, both cooperation and competition come into play. This dynamic is a feature of ecosystems in general. Thus, going a little deeper down the present rabbit hole, it seems only natural, from both the above dynamic point of view and an evolutionary stance, that, at the cellular level, invading pathogens (bacteria, molds, and such) would find it adaptive to put the components of the IS off their stride, to mess up their tightly bound "orchestration". That is, to bring about dysregulation. (Beyond HIV/AIDS, which is infamous for trashing the IS, this has not been particularly well studied; nevertheless, many staphylococcal molecules are known immunomodulators.) *All* life wants to live; though whether through cooperation or competition, or both, depends on the organism and the context. (This dynamic leads to an inevitable arms race, a standoff sometimes called the Red Queen Effect, a term popularized by Matt Ridley, but originating from an observation from the Queen of Hearts, who argued that "it takes all the running you can do, to keep in the same place." In this regard, it seems to me that unilaterally quitting the race, i.e. unilateral disarmament, leaves a wide-open path for the competition that refuses to lay down arms.)

In this way, my own view of immune disorders, including all autoimmune diseases (AIDs) and surely most cancers, is that they must be about some regulatory failure in the IS, probably along with other systems. My stance is that the preferred remedy is to reestablish a homeostatic balance among the populations of various leukocytes and cytokines. I understand the principle that, if "conversion" is not possible, the only recourse is to "kill 'em all", usually through chemotherapy. (If McGiver knows a watch is set to trigger an explosion in a crowded mall at, say, noon, then the one potential solution remaining just before the appointed hour must be tried: Remove the device's battery, if possible, or, take a maul to the thing—desperate moves, to be sure, since they may hasten rather than avert the cataclysm, but a necessary one.)

And yet, this is, at best, a temporary solution to a larger problem. To utilize that strategy repeatedly is folly, and cannot be sustainable. (Freud's definition of insanity? Doing the same thing over and over and expecting different results. His aphorism is often cited in self-help programs; as an aside, please allow me to gently observe that doctors can become addicted to treatments just as abusers to their substances, though, one hopes, without the pathos. In fact, paradigms are shifty beasts, just like the data they are presumably based on; if there is is one thing that should be common wisdom it is that many ideas may be common without being wisdom. [I remember finding a particularly remarkable—in retrospect—example, an ad in the October, 1929 *Scientific American*~ that mirrored the common wisdom of the time, to the effect that four out of five doctors recommend Lucky Strikes!] Yet, how much should we mistrust trust?) Moreover, there are other potentially deleterious complications, at both the cellular and the organism-in-context levels. Chemotherapeutic immunosuppressive agents such as cyclophosphamide are intrinsically toxic to many body parts and systems, often leading to a lot of collateral damage. But ignoring this for the moment, a successful treatment is the equivalent of slipping the IS a Mickey Finn. With no soldiers around, it doesn't take the insurgents long to wreak a lot of havoc, damaging the body even further (likely triggering a new round of inflammation from whatever is left of the IS, necessitating yet another bashing...). Then too, dismantling the IS removes the main line of defense against not only the invaders and the bad natural-born citizens, the mutant cancerous cells,

but also removes the security forces protecting "law" abiding" normal cells and "green card aliens". Thus, the "middle class" is beleaguered, and the risk of cancer skyrockets. The risk of anemia is about 100 percent, as immunosuppression also suppresses red blood cell production in the bone marrow. A personal "side effect" was dysgeusia—badly functioning taste buds. It is a good thing that I don't earn my keep as a chef or food critic!

The Hair of the Horse

So we are dealing, as my doctor puts it, a double -edged sword: If one side doesn't get you the other will. But it's worse than that. The sword is, to us, its targets, like that of Damocles: ever hanging existentially over our heads by a thread.

Well. Living with infections or malignancies is not sustainably human. Neither is living in a sterile bubble. Unlike rocks and other inanimate objects, we cannot just, as the King of Hearts advises Alice, "[b]egin at the beginning and go on till you come to the end; then stop." Being human, in the sense I mean, requires the full complement of feelings and emotions, with a bias in favor of joy over despair, encouragement over discouragement, happiness over sadness, fulfillment over failure, empowerment over impotence, participatory usefulness over aimless somnambulism. (I'll say more about humanity in my concluding remarks.) There is lot to say for "feeling good", but harsh therapies stifle much of that conversation. Indeed, feeling good, in my sense, can be, as several lines of evidence suggest, powerfully therapeutic, in and of itself, both indirectly—mediated through neural processes—and directly through molecular signaling. More of this later. Doctors do sometimes mention, in passing, "quality of life" issues, though one hears this as cliché; it's like listening to lawyers discuss ethics: They once took a class on the subject. In any case, this discussion almost never gets to the the root of what constitutes quality or even what constitutes "life", as humans practice it. (One frequently overlooked complication, in this regard, is the expense of medical treatment. Even with insurance, there are co-pays, co-insurance, deductibles, drug costs, transportation and parking, all in addition to the time spent not working. [I'm of the opinion that free lancers should never get sick. It is too hard to keep up the nearly 24/7 work schedule needed to earn one's keep!] All this makes the challenges of being human even more difficult, even while the engine for living a quality life may be running on fumes. This is a time, after all, when the patient has scant redundancy and emotional reserve available, and, in attenuated states even those remaining are overworked by "extraneous" considerations, like medications, anemia, fatigue, and new infections. No wonder that depression often sets in, leading to a vicious downward, often literal death spiral. Frankly, I don't know how anyone with a serious illness can make it without a strong and supporting family, however "family" is defined.)

Into the Looking Glass

In my view, rebalancing the IS, then, is strongly preferred over its dismemberment. But is this, given our present state of knowledge, a possible and feasible clinical strategy? Perhaps, though a reasonable working definition of "feasible" clearly depends on one's position along the dogma/heresy continuum. As for getting to "possible", that has been, for me, something of an Incredible Journey through Wonderland, and would have been even without even without the Lewis Carroll allusions.

The synopsis of that odyssey of discovery is this. At the cellular level, things get pretty complicated, what with all the granulocytes (neutrophils, eosinophils, and basophils), the various lymphocytes (the T-cells, B-cells, and natural killer cells), phagocytes (macrophages and monocytes), dendritic cells, and, along with chunks of proteins that make up hormones and enzymes, cytokines and chemokines that serve as catalysts, messengers, and homing beacons, among other things. Not only is there widespread two-way communication among most cell types (those of the IS, of course, but also the endothelium [the cells that line organs and blood vessels]), and, most famously, the nervous systems. The amazing thing is that the complex as a whole self-regulates, partly through influencing gene expression (that is, which genes are turned on or off, and under what conditions.

For a detailed example, nuclear factor kappa Beta (NF-kB) is known to up-regulate the gene that expresses Interleukin-8 (IL-8). IL-8 is a chemokine (a small cytokine) that is, among others things, pro-inflammatory. Through chemotaxis, it guides other components to the battle zone. Fine; inflammation is a normal and necessary process, at the right time and in the right place. But when the job is done, something needs to turn off the machine, but what if the normal regulators of NF-kB, one of them the p38-MAPK enzyme, are themselves dysregulated? (What if the sorcerer gets clobbered by a train while on holiday?) At this point, IL-8 levels soar; the upshot is that inappropriate inflammation also soars. Oh, and IL-8 is also involved with angiogenesis; its high levels allow active tumors to quickly develop internal vascular systems.

Is it enough to simply inhibit NF-kB production? That might, possibly, help retard AIDs and some cancers, but it surely cannot be the full answer. It is just a small part of the puzzle. My own ailment is classified as Wegener's granulomatosis, an AID that is of a class of small and medium vessel vasculitides. The full description of the genre is pauci-immune (referring to the paucity of histological hypersensitivity evidence) ANCA (Anti-Neutrophil Cytoplasmic Antibody) Associated Vasculitis (AAV). (I believe that, given the consensus nomenclature, symptoms, and histological evidence, the better diagnosis in my case is possibly Microscopic Polyangiitis, MPA. But what's in a name? The standard therapy remains the same, though there may be additional concerns, as MPA is associated with a slightly higher risk of coronary complications.) How ANCAs come into being and become, possibly, pathogenic is a long story involving, in part, various lymphocytes: T-reg cells, T-memory cells, B cells, and dendritic cells. And these come in several different flavors, classified according to protein receptors on their surfaces.

For unknown reasons, whatever regulatory mechanism that optimizes the relative populations of these cell types is, in AIDs, on vacation, possibly permanently. For instance, we see in AAV diseases an abnormal proliferation of T cells with the CD4 receptor, but without the CD28 receptor. Such T cells are associated with "anergy", the inability to mount a proper immune response. In any event, certain enzymes are stored in neutrophils. (ANCAs are classified according to the enzyme antigen they attack, usually Proteinase 3, PR-3, or, in my case, Myloperoxidase, MPO) These are normally are used to promote apoptosis (cell death) of cells infected by a pathogen, but end up inducing damage to and apoptosis of normal cells. (Monocytes also produce PR-3 and MPO, and can become the

target of ANCAs.) Now, MPO and MPO enzymes do their job in large part through "respiratory bursts", the release of ROS, reactive oxygen species. When they have fulfilled their legitimate work, they need to clear out; otherwise they can cause "bystander injury". In the case of MPO, this generally requires the services of plasminogen, which for undetermined reasons seems to be in short supply in many AIDs. Much of the damage in this cascade seems to be in the apoptosis of the MPO-bearing Neutrophils. These moribund cells release their deadly cargos in close vascular quarters and clog up small vessels, sometimes causing thrombosis.

ANCAs are usually of IgG (Immunoglobulin-G) type, with a few IgM and IgA types thrown in. IgG types come in four sub-types. In AIDs, the ratios of these subtypes become much different from normal. No one knows why. They are produced by B cells. Are they directly pathogenic pathogenic or merely a marker? There is controversy about this. Howbeit, we already have a huge cast of characters, having said nothing about the involvement of Tumor Necrosis Factor alpha (TNF), various cell adhesion molecules, Beta 2 Integrin (which mediates Neutrophil adhesion), human LAMP-2 proteins, IL-6, IL-2, Interferon gamma, and several relevant genetic factors. Though hardly bit players in this drama, you already get the point of this exposition.

A Menagerie of Beasties

What stimulates all this dysregulation? Mostly, according to consensus, infectious pathogens. *Staphylococcus aureus*, a species of gram-positive bacteria, is a usual suspect. So are certain some fimbriated gram-negative bacteria, such as many strains of *Escherichia coli* (in addition to inducing IS responses, some *E. coli* strains produce nasty toxins that cause grave damage to kidney cells); cytomegalovirae (of the herpes group, which includes *varicella zoster* which causes shingles in humans) are also a possible direct or exacerbating culprit. Environmental factors can come into play, particularly silicosis (asbestos poisoning). Lyme disease is another ANCA associated AID. Its diagnosis is notoriously difficult, though its specific etiology is well established (its pathogens are species of tick-borne *Borellia* bacteria). But for most other AIDs, there are too many possible etiologies to make a definitive accusation.

Clearly (so to speak!), there are many possible vectors, many possible trajectories, for disease development. Indeed, many pathways are likely in operation for each individual case. Adding all this up makes the head spin and fizz in a reductionist's migraine. It's hard to see the *trees*, let alone the forest. But before we say, "blow it all up, and let God sort out the mess", let's take a step back and consider whether a less reductionist view might suggest a safer and friendlier approach—perhaps even a more efficacious one.

Out of the Hole?

Present therapeutic regimens for diseases like mine call for two phases of action. First, blast the IS with, usually, cyclophosphamide, along with large doses of prednisone, a corticosteroid, to further modulate the IS and cut down inflammation. Second, attempt to keep the disease, or at least its symptoms, at bay. The general idea here is to either a) hope

for remission, or b) keep the IS suppressed. In this stage, "slightly less" toxic immunosuppressors are preferred, commonly azathioprine or methotrexate, though sometimes oral cyclophosphamide is ordered. These two stages are called, in amusingly sterile clinic-speak, Induction and Maintenance. All the above heavy drugs are nasty, dreadful, and potentially dire, associated with uncomfortable probabilities of mortality and morbidity—a.k.a. death and destruction—along with extra stress on the organs they are assigned to protect. Even prednisone has its, uh, quirks. For me, these included, at least at the higher doses, shaky hands, unusual cramping, cataracts (oh, yeah—another expense), and extremely vivid, long-form dreams. In refractory cases, those that respond poorly to standard regimens, other pharmaceutical remedies might be employed. Some examples are Rituximab, Mycophenolate mofetil, and, less commonly, deoxispergualin. There are other "conventional" possibilities (meaning, in effect, drugs that bring high profits to their patent-holders) in the works, mostly other monoclonal antibodies (those drugs that end in -"mab"), like Infliximab, which targets TNF-alpha. In theory, MABs can be designed to focus on any specific component. Good idea, maybe, though they all suffer from two problems: largely unknown and potentially disastrous complications, and ruinous expense that insurance companies are, understandably, loathe to cover. As noted, the idea with them is not to "kill 'em all" so much as to kill some subset. That is, they are more targeted. Still, there are plenty of more generalized risks involved. For one thing, the problem may not go away (you can take out Osama bin Laden, but does that destroy al Qaeda?) Also, they are still immunosuppressives, so risk of infections remains high. Eculizumab, for example, targets the alternate complement pathway, C5, the blocking of which, at least in mice, prevents necrotizing crescentic glomerulonephritis—renal failure that is a common feature of AAVs. Promising, yes? Well....Soliris, the trade name of Eculizumab, sold for an entirely different application, comes with a caution to be sure you have an up-to-date inoculation for meningitis (!), and has been described as the world's single most expensive drug, which is saying something. Hah! Try talking the insurance company into paying for *that*...for off-label use, yet! Inoculations of all kinds, by the way, are a bad idea for those under immunosuppressive treatment programs. Inoculations are all about inducing an IS response —exactly the opposite of the intent of immunosuppression.

(A note here about "targeting" and "side effects", two more safe, clinical terms which needs unpacking. A "side effect" is, in fact, precisely "missing the target". If you aim to shoot an apple off your kid's head, there is a finite but known substantial risk of missing the apple and putting out an eye instead. In writing and talking about medical matters, this would be a considered a side effect: You missed the target. But, really. the danger was, and always was, some statistical probability. [Like all probability waves, this too will collapse when it hits reality. The sword of Damocles sometimes falls on the noggin of Schrödinger's pitiable cat.] Perhaps a better image is of blasting the apple with a shotgun: You get the apple, all right, but end up taking out a lot more than that. An even better image in some cases: The apple is firmly glued onto the scalp, so even if you hit the target dead-on, you rip away what you were trying to save.)

Can we do better than *deus ex machina* on the one hand, or on the other, a perpetual game of whack-a-mole?

Making the Deal: *A Tale of Doors*

How about true out-of-the box alternatives? Naturally (so to speak), I have been offered suggestions from friends who are well-meaning, but with varying degrees of legitimate qualifications. Mostly, they draw their information, such as it is, from the same fountain I do: Internet searches. Frankly, while I will listen to most anyone, I must trust my own reasoning more than theirs for the following reasons. The Web is a terrific boon for learning. Yet when you are attempting to acquire specialized knowledge, there are some cognitive barriers to hurdle: learning how to read the literature with its peculiar style and jargon, and figuring out how to cross-reference in order to understand assumed prior knowledge. Besides, much of the technical literature is unavailable without a financial outlay; often, only the abstract is free.

Still, there are vast quantities of material Out There. The trick is to separate the curds from the whey. This isn't always so easy. With much of the accessible stuff there is an underlying profit motive, which can be explicitly stated or may be obscured. (This doesn't necessarily preclude utility, but it does suggest that additional corroboration is a good idea.) Even the dry, academic, technical literature suffers from this problem, though more discreetly and indirectly. In science, the game is to ask 20 or more questions of nature, one at a time. But how do you decide what questions? Keep in mind that nature is not obliged to tell you, the researcher, whether you asked the relevant ones. The decisions of what to ask do not come out of thin air, but are related to one's pre-existing world view, the professional/social milieu (ideally, you want to ask the questions before the next guy asks them), and, perhaps most importantly, where the grant money is coming from. If there is a bias for pharmaceutical approaches to medicine (and there indubitably is), there is a reason for it: Nowadays, most research is sponsored by Big Pharma. That's where the money is, and so, regardless of the integrity of individual researchers, the end result of all this has a profit motive. Even more covertly, perhaps, is the fact that the journals take in most of their advertising from Big Pharma, and many are actually owned by publishers who serve Big Pharma in other capacities. Indeed, many influential papers have been written by ghostwriters who have never seen the raw data, but only the summaries provided by the drug companies themselves. A further complication is that many of the regulations covering pharmaceuticals were not written by actual legislators (what would *they* know, anyway?), but by the companies who stand to benefit from them. Even the FDA itself relies on fees paid by the companies. Again, this is not to say anything about the probity and rectitude of individuals involved or the accuracy and appositeness of the results. Nevertheless, since the system as a whole has "homeostatic" needs (i.e., profit) that may be—indeed, *must* be— vastly different from that of actual humans, it behooves us to be wary in interpretation, and not only read between the lines, but past them as well. By contrast, with most alternative approaches, the profit motive is usually explicit (usually in the form of "buy supplement X; it will solve all your problems"), or non-existent, though in both cases most of the supporting arguments tend to be poorly stated or documented, relying heavily on testimonials and first-person reports. Well, everyone is a huckster of some kind; we all need a gig. Yet I will confess that I find attempts to sell me ideas alone are more charming than those that want a piece of my estate—even

though most ideas are memorable about as long as your average dream. (A few, though, might change the world.) This is to say, again, that, some form of corroboration is needed.

In fairness, I have to include patient participation in the overall dynamic. "Consumers of medical services", as some politicians put it, understandably want the most "bang for the buck", which, in this context, means the most dramatic results given the few minutes the insurance companies allow the doctor to give you. Drugs, therefore, win out by a wide margin over anything else. For those who don't trust doctors, the *promise* of supplements or other panaceae serves the same purpose. At some point, of course, the limitations and drawbacks of either approach become all-too apparent. (If your car is burning oil, replacing the head gasket may be the best long-term solution, but simply topping off the oil occasionally is far cheaper in the short run. Come to think about it, the auto mechanic metaphor might shed light on how many patients view medical services these days: "Fix me up, Doc. Oh, and I'll need my body by the time you go home. I need to go to a party tonight.")

Having said all that, I will try to interpretively summarize what I have found in the way of "alternative treatments".

Eat Me

Diet: Yeah, well, easier said than done. Most of the nutritional advice have been promulgated by and for already fairly healthy people—at least in the sense that they have, as yet, no major organ damage. "Eat more tomatoes, with all that prostate-saving lycopene!" "Nuts are great sources of magnesium!" "Avocados have the *good* fat!" "Tofu is non-dairy!" All true, of course. But for those with, say, already distressed kidneys, the game is not to eat more of anything, but rebalance the intake, minimizing (in moderation; clearly, it is possible to go overboard with anything, including abstinence!)) those ingredients that put a load on the poor things. These include sodium (salt), potassium, phosphorous, and magnesium. Wow! What's left? To top it all off, high protein diets have been shown to expedite the need for dialysis. These restrictions can be brutal for meal planning. True, there are nutritionists available for consultation, but, in my experience, their advice is often incomplete, ambiguous, misleading, or plain wrong, sometimes with too much detail, but more often with not nearly enough. Once again, your own research is mandatory. (Are data "better" than one's own gut feeling? Not necessarily. How do you know the questions asked to get all those data were the right ones?)

(I feel compelled to point out here that, though personal research is required for optimal utilization of medical services, this is not possible for many patients; spanning the knowledge gap is a bridge too far, especially for sick people—and what, only healthy folks should ever get sick...? I personally would go for a system of independent patient advocacy. Only, who's going to pay for it? In the old days, when most daily medical needs were met by the "family doctor" who regularly provided long consultations and knew your complete history—including, possibly, your grades and whom you were dating—was the intermediary with required specialists, and may have even made house calls, there was little need for a

separate advocate. This is no longer economically realizable with the modern specialist system. Even "primary care" is now a specialty. Any professional advocacy, such as it remains, it typically outsourced to yet another specialty, "social services". Within this system, no patient can have a true advocate outside friends, family, or him- or herself. And there self-interest and the knowledge gap, and the not-uncommon condescension on the part of the professionals, meet in an unholy disunion. I hasten to add that, while it is true that some physicians come by their patronizing naturally, many others use approaches that seem lofty, to the patient, because it's easier that way, given the huge disparity in knowledge. In my business, an enthusiastic client often comes to me with a suggestion for microphone placement after, perhaps, reading an article or two. I sometimes have to very consciously take the time consuming role of colleague and educator rather than avatar, a mouthpiece for the gods. [Sometimes, it helps to mock myself, by saying that everyone at my level of expertise is arrogant; the difference is that, in my case, that arrogance is justified.] But I can choose to do this; it is more difficult when you have have a full clinical staff to support.)

Eating out is problematic, considering that restaurants' stock-in trade is largely salt, sugar, and grease. This is true even at the healthiest joints. That beautiful soup? Ooh--salt festival! A nice juicy steak? Charred flesh slathered with butter on top of salt on top of butter....Sea salt? Salt with contaminants. Cheeseburger, fries, and a shake? Are you kidding me? Even if the menu looks okay, when you live in fear of dire infections, it's easy to stress over kitchen sanitation, the source of the ingredients, and the hygiene and contagiousness of your neighbors.

Steroids can push glucose levels into the near-diabetic range, so it pays to watch the intake of sugars. Some sweet things contain high proportions of sugars other than sucrose (plain sugar). They have a lower "glycemic index", meaning that they are converted to glucose for bodily fuel more slowly and hence do not induce a strong "spike". These include blue agave nectar and most fruits. Still, they are all end up as serum glucose. (Do you know how much sugar is in a 16 oz. bottle of your favorite soft drink? And how much phosphorous?)

Lakes of Fire

"Natural" anti-inflammatories: Yes, fish oil, olive oil, and flax seed oil, among other products, are anti-inflammatory, and by all accounts are "good for you" on a variety of grounds, largely related to cardio-vascular health. They do not, however, represent a panacea. Neither are their anti-inflammatory properties sufficient to whack down the kinds of inflammation generated in AIDs. Some herbs and spices, such as garlic, cinnamon, and tumeric are often promoted in this regard. Indeed, those of us with low-salt diets tend to use a lot of these products in cooking. But gustatory amounts fall far short of suggested "neutriceutical" dosages, which might be a good thing: Little is known about large-dose toxicity or interactions with all the other chemicals we shop-vac into our maws. Or even whether exogenous anti-inflammatories as a class are actually efficacious. DHA, the omega-3 oil found in some fish, seems to work appreciably well, if not dramatically, though this is not clear in other cases.)

Not-so Blithe Spiriting

Anti-oxidant therapy: Reactive oxygen species play a vital role in many life-regulation processes (as do reactive nitrogen species). For one thing, "free radicals" are a major tool employed by the IS to deal with malignant cells. However, the process must be constrained, lest the damage extend to innocent bystander cells. The bodies of nearly every living thing produce endogenous anti-oxidants for this homeostatic purpose, principally superoxide dismutase (SOD) and glutathione peroxidase. They work a little differently, but often synergistically. Thus, the supplement industry has been for years touting the benefits of a huge smorgasbord of exogenous anti-oxidants, from vitamins A, C, and E, selenium, and a wide variety of often exotic plant parts. More recently, glutathione pre-cursers such as N-acetylcysteine have become popular. The idea here is to stimulate endogenous glutathione production. Glutathione is itself useless taken orally. It wouldn't survive digestion, and, even if it did, its molecules are too big to enter the cell; it has to be manufactured "on-site". (SOD, by contrast, comes in several forms, and is found both circulating and in the cytoplasm.) Cysteine molecules, on the other hand, are smaller and may provide important raw parts or catalysts for glutathione production.

Another antioxidant that is widely sold as a supplement is CoQ10, a fat soluble compound necessary for mitochondrial adenosine triphosphate (ATP) production (see below). However, it is far from clear that endogenously produced amounts are inadequate, even in sick people. As they say, more research is required. Indeed, it isn't at all apparent that direct scavenging of free radicals is actually therapeutic. After all, what protects the good cells may protect the bad ones at the same time. In any case, there is likely a Goldilocks principle at work with most things the body can synthesize on its own, and adding extra probably does little to alter this—at least for healthy individuals. And picking out deficiencies in other cases is not always so easy. Finally, products sold as anti-oxidant often have therapeutic effects, though not always the purported effect, and not always through the purported mechanisms.

We can summarize the above issues this way. Ingestibles can be classified as "raw parts" and "medicines". Raw parts might be water, proteins, fats, electrolytes, most vitamins, and trace minerals. They are required because they cannot be synthesized in the body, though, once there, they can be used to synthesize other necessary products. Medicines are ingredients specifically introduced to alter some state, possibly of disease, but not always (caffeine—the example comes to mind at the moment, as the person in front of me at the coffee shop just ordered a five [!] shot carmel macchiato—can, in my scheme, be classified as a medicine, though what it "cures" is not a disease in the normal sense). The digestive system works very well with raw parts, and less well with medicines, which generally need to get through the digestion process without much degradation. (Most medicines are taken orally, for convenience, though they are usually more efficient taken intravenously or sub-cutaneously.) For raw parts, "dosing" is not usually an issue for healthy people, the theory being that the body can just slough off what it doesn't need. The same principle holds, partially, with medicines, though with a much tighter tolerance. Thing is, though, the organs chartered to discharge the excesses, the kidneys and the liver, can become stressed under disease conditions, so the too-much-is-about-right approach falls apart. (Symptoms such as night sweats and itching can be interpreted as a desperate attempt to recruit the skin as an

auxiliary organ of excretion.) This is true for both raw parts and medicines. Complicating this issue is the fact that "medicines" do not always use the presumed mechanism for their actions; they may work, but not in a direct way, and not always with the intended results. Or they may not work at all.

Overall, the research does not provides tons of encouragement for therapies based on supplemental anti-oxidants (except, in some cases, for protection of neural cells), though there is an intriguing likely special case, over-the-counter to boot. A fair number of studies support a consideration of the therapeutic use of certain lipoic acids, the best known being alpha lipoic acid, ALA. It is claimed to be "anti-oxidant", and it is, at least in context, though its actual mechanism seems to be through a *pro*-inflammatory pathway, triggering a production of the endogenous anti-oxidants. This "rebound effect" also appears to be behind the salutary qualities of the mildly toxic cruciform vegetables—"eat broccoli! It's good for you!"—and aerobic exercise, which provides a fair amount of oxidative stress to the body. (A short parenthetical aside here: Many homeostatic mechanisms work via this "rebound" method. Resistance training, for instance, creates micro-tearing of muscle tissues, inducing repair teams to rush in and make the muscles stronger in the process. But this makes perfectly good sense as a principle: Nature is frugal; if you don't need it, why waste the resources? If you do, invest! Trees never move, so why would they need a brain? All they need to compete in their world can be accomplished without a single neuron. So: challenge-response as a tuning device is a major player in homeostasis. Not so incidentally, this, I think, is why the "kill 'em all" philosophy is unsustainable: You can only *suppress*, not completely wipe out, any opposing population, whether it consists of bacteria or religious sects or ideas. Again, *all life wants to live*, and a suppressed population may come roaring back with a deadly vengeance. And even if you actually *have* managed to kill 'em all, there are always new forms waiting to fill the vacant ecological niches.) In addition, ALA may act as a catalyst of sorts. Vitamin C is water soluble; Vitamin E, in its various forms, is fat soluble. Neither one, by itself, contributes much to the glutathione/SOD situation. Together, they work synergistically, and ALA seems to potentiate (strengthen) that synergy.

Mitochondria, the real working class of cells, have a different genome, with different DNA, from that of other body cells (these organelles—subunits of the cell with specific functions—were probably independent bacteria at one time in evolutionary history, but now have their "green card" and perform a lot of the cellular hard labor, particularly in what we might call the energy sector: producing ATP for both domestic use and export) and utilize a different kinds of SOD (based on manganese) than normal eukaryotic cells (based on copper/zinc; even bacteria use forms of SOD, commonly based on either manganese or iron). Without mitochondria, we, as vertebrate mammals, couldn't exist, any more than plants without chlorophyl. (Yes, I know that some plants do not contain chloroplasts. But they find a way: Many mushrooms, for example, have very high levels of SOD. Indeed, some exoteric species are marketed as "medicinal herbs" for alternative cancer therapies. All I have to say is about this is *caveat emptor*.) It pays to take care of the labor class. In any case, there is speculation that ALA bridges this SOD gap as well. I'd put ALA in the "can't hurt, could help" category, though what provides a therapeutic dosage seems to be strictly anecdotal at this time.

Spandrels and Vistas

Speaking of bridges, the ALA conversation might, possibly, get us to the higher abstractional viewpoint I have been circling around: a matter of balance, which takes the gold, for purposes of this essay, as the top universal metaphor. From here, we can focus our binoculars on a more more general IS regulation. You see, a common misperception is that, in autoimmune diseases, the sufferer's immune system is "too strong". Looking at the big picture, this is misleading, in the same way as it is wrong to claim that the choir is too loud just because a couple of tenors bellow. The problem is, as I have earlier suggested, one of dysregulation. Zooming in, it appears that lines of communication (probably chemical/genetic, but possibly neural) get trashed, allowing proliferation of components that have no business proliferating then and there.

What I am seeking, then, is a complicity of bottom-up *and* top-down dynamics to rebalance the entire IS, or at least modulate the components that have gone hog-wild. Is there a chance of this? Maybe. My trek eventually led me to a contender—a long shot, perhaps, but it could be worth a flyer. (An even longer shot, and hence not worth a flyer at present, but perhaps worth mentioning: Coming out of HIV/AIDS research is the possibility of essentially destroying the patient's IS, then rebuilding it from the ground up, as it were, with blood marrow stem cells from a healthy donor. This may indeed become a viable mainstream therapy in the future; for now, it is impractical, both because of the hideous expense and the difficulty in choosing the right donor for such custom treatments.) This is a novel pharmaceutical treatment called LDN, low dose naltrextone. I say "novel" because it isn't widely known past an enthusiastic collective of clinicians, researchers, and patients. Naltrexone is a drug, now off-patent, that was originally developed, approved, and still used to treat addictions to narcotics and alcohol. It is an "opioid antagonist". The body produces its own opioids, the enkephalins and the more renowned beta endorphins—those hormones that make you feel good. Naltrexone works by blocking the cellular opioid receptors. Fine for addictions, but how does this affect the IS? Glad you asked. We think of endorphins as being local to the brain and nervous system, but this is not so. Opioid receptors of at least three types, labeled mu, delta, and epsilon, are found in nearly every cell of the IS. The opioid agonist/antagonist system is pervasive, and may be something of a global modulator for the IS. Interestingly, patients with AIDs and many cancers have a much lower than normal endorphin level.

Here's how LDN is supposed to work: The standard dosage for addiction treatment is 50-100 mg. per day (depending on body weight and other factors), in slow-release form, thus blocking the opioid receptors for long periods, denying the pleasure rush the addict craves. By contrast, LDN dosages are on the order of 3-5 mg. per day in fast release form, usually taken at bedtime. This blocks the opioid receptors for only a few hours. But by morning, a rebound effect has taken place, and will last the rest of the day. Extra endorphins are produced to approximate the levels found in healthy people. LDN also seems to be as potent an anti-inflammatory as prednisone, without the latter's side effects. But what are the side effects of LDN? At least at that low dosage, the only thing noted is the occasional sleep issue, including vivid dreams—to which I say, "so what?" I get that from prednisone anyway. (There is a specific contraindication, however. When immunosuppressives are used expressly to prevent transplant rejection, LDN may confuse the process.)

The main drawback, other than its relative unfamiliarity, is that it needs to be provided by a compounding pharmacist, a service that few drugstores provide. As to the unfamiliarity, there are several reasons for this. In the first place, LDN is an off-label use of the product. There is nothing illegal or unethical about prescribing off-label, but many doctors are skittish about doing so, for two reasons: professional accountability and personal style (see my previous comments!). Then too, since the drug is out of patent (and is already FDA approved anyway), there is little incentive to spend the huge amounts of money to do the R&D needed to re-certify the product for a novel use, especially when the same investment can finance development of a newer, patentable, and hence more profitable drug. For the same reasons, it doesn't pay to have sales reps promote such uses. So most of the scant research on LDN has been privately funded (in some cases by the investigators personally). So far, the formal studies have been limited to Crohn's disease (an inflammatory AID of the intestinal tract), multiple sclerosis, and fibromyalgia, with pilot studies showing positive results in HIV/AIDS and pancreatic cancer. However, there is a larger body of case studies that cover many more cancers and AIDs, including Wegener's. Though inadequately documented, in my opinion, they are, in collective form, encouraging enough for further investigation. On this basis, I would also put LDN in the "can't hurt, might help" bracket and would be willing to be a subject. (Meaningful horizontal case studies are tricky to design and make intelligible, but can be useful tools nevertheless, given enough numbers and clever statistical interpretation. At least, they can help generate new hypotheses and provide the impetus for more focused investigations.) In any case, there is, as I've said, a lot to be said for feeling good...!

By the way, there is a related alternative therapeutic technique, involving OGF, opioid growth factors. But, though making the rounds of the alternative therapy websites, it is even less known than LDN, less convenient, and more difficult to pull off, as it is not sold in direct form in this country (some drugs that upregulate endogenous OGFs are commercially available, however), and must be administered intravenously. Its pathway uses a different receptor, now called the zeta opioid receptor. So far, the formal studies have shown some positive benefits in treatment of pancreatic cancers.

The Thumb on The Scales of Time

"Balance", in the sense that I have been using the word, is very old. This archetypical metaphor was surely ancient when the Preacher intoned "To every thing there is a season, and a time to every purpose under the heaven...." Perhaps it goes back to beginnings of life itself—or earlier. As I've tried to make clear, I conceive of *balance* as the equivalent to homeostasis across all levels of abstraction. Though stimuli and vectors vary, the concept, to me, is fuzzily axiomatic ("fuzzily" because ambiguity is embedded in its formal description!).

We have been so far discussing, mostly, homeostasis as it relates specifically to the IS. The nervous system, consciousness, and the mind, too, must have evolved to solve problems of homeostasis, to tune organisms into balance; otherwise, nature wouldn't have bothered to spend the resources, brains being very costly in a metabolic sense. Thus, it is reasonable to wonder whether acts of will, or at least acts of non-conscious neural processing, can modulate the IS. We do know that many neural processes are correlated with internal

physical states and processes, either by acting on muscles or through chemical intermediaries. In most regulatory cases, there seems to be no conspicuous conscious linkage, however, no evidence that an act of will can directly influence immediate life-regulation. This makes a good deal of sense: it would be a bad idea to have to think about every little detail before regulation could be accomplished.

Breathing, though, cuts both ways; it can, at least in humans and marine mammals, be either automatic or voluntary. So, perhaps, as Qigong enthusiasts maintain, breathing is a bridge between the self and homeostatic balance. Whether or not this obtains, however, it is certainly true that conscious decisions can act indirectly on all body systems, through altering the internal and external milieus, the person's contextual "operating conditions". Exercise of various sorts; moving to a new city; leaving a deleterious relationship; heeding the doctor's advice (or not); self-medicating through use of alcohol, narcotics, or dried vegetable parts; singing in the choir; making dietary choices—these are all examples of an attempt to establish homeostatic conditions for one's whole organism. Given that this is all done with limited knowledge and in a social context, competing and cooperating with others in the same boat, as it were, this is all a tricky business, and meets with varying degrees of success and failure. Still, a reasonable balance does not require perfection in this regard; for mortal creatures, it is enough to be just successful enough for just long enough. Speaking for myself (of course!), I do not subscribe to the notion that anyone can just talk themselves into a better mood or higher self esteem. That is not the kind of emergent "top-down causation" that consciousness appears to have evolved for. (I could be wrong, of course, though our understanding of brain architecture and its feedback/amplification loops does not, yet, support the counter-arguments.) It is, I think, far more likely that transient dispositions and moods of mind (as well as many innate ones) well up from bodily states and their chemical correlates, the famous neurotransmitters and neuropeptides more than the other way around. (By the way, medicines work, when they do, by altering the [internal] operating environment. Allopathic medicines—the kind your regular doctor is most likely to prescribe—usually act directly; homeopathic medicines tend to be indirect, inducing some bodily response.) Again, however, the *larger* feedback/amplification loop *can*, and surely *must* include conscious acts of will. A conscious decision to stay out of harm's way, to avoid a confrontation with a belligerent drunk, say, or where to eat dinner and with whom, affect's one's bodily states and processes as surely as pre- and non-conscious reactions, and with more of an eye to the future. And by now, we've all heard of laughter therapy. There is some controversy about how this works, but putting oneself in an uproarious situation might help —unless it doesn't.

Star Roving: *The Abode of Mortals*

I want to conclude these ruminations with a few comments about what it means to be human. Interacting with domestic dogs and cats, watching corvids and marine mammals at play, and studying the complex behaviors of other primates and elephants, it is difficult to believe that we are the only species with an autobiographical self. I am prepared to believe that humans are not alone in this sense, though from our point of view, cutting-edge in an evolutionary sense. Where we do seem qualitatively unique, however, at least from my perspective, is in our sense of dimensionality *through time*. It is often said that evolution is not teleological; it knows nothing of, and cares nothing of the "future". I would argue this

point: *We* care about the future, and we are creatures of evolution, so some "primitive" for teleology must be embedded in the evolutionary flow somehow. In any case, here we are, with a sense of meaning in both the past and the future, along with the moving picture we call the present (and, then, there we go).

Stuart Kauffman writes of life finding a "home in the universe". I believe this to be a profound, and profoundly numinous stance, though "home" may imply something of a territorial sanctuary, a fixed location in space. Humans, though, are restless, incessant doers, creators, imaginers, and, come what may, explorers. We are designed to posit and investigate worlds that have never been; aware that most never will be. God's garden, we might say, has many paths. (This sounds Borge-ian; "In my Father's house there are many rooms" is the Biblical version.) In the "space of all possibles", what arc through eternity do we choose? Not even God can, within time, foresee. It is in this *trajectory* that we find our home in the universe. And it is to know what and where this home is that we have evolved our skills at perceiving depth, including deep time. (And in this skill set I am including the emergent senses of language and metaphor as well as the classic physical senses; indeed, even those persons whose physical modalities are compromised usually seem to retain the feeling of depth.) Yes, I am aware that there are individual differences. Some would rather tidy up their own cave, while others can't wait to explore an unknown valley. We all fall along this continuum, though the thrust of humanity favors the restlessness, the journey.

In the spirit of triangulation to decode what I am calling dimensionality, let me get at this "home in the universe" bit from another direction. I do not see the source of language, as humans practice it, from a Chomsky-like position: Structure, I think, did not come first. Rather, my working hypothesis is that language emerged (and is now "hard-wired", at least in the spoken version) from the complicity of two "primitives": narrative and metaphor. Narrative deals with subject, object, and, especially, action. (The structure-as=primitive hypothesis relies on narrative, but out of time, which makes no sense for temporal creatures.). Metaphor provides the temporal stance, the contextual depth and the critical "fuzzy logic". It is what, in human implementations, allows the abstractional plasticity to sense (and swim in) the river of history and our own autobiographical place in its eddies and backwaters.

Again, insofar as the future is concerned, it is not perfect prediction or control we are after. It isn't going to happen; a "God's-eye view" is not possible (again, within time). Rather, *it is in the feeling that we can choose doors and pathways* that we become truly human. (This is surely adaptational in the Darwinian sense. I believe, moreover, that, as a "primitive", it is specifically behind the emergence of the top-down causation that make consciousness an adaptation.)

There are clinical implications for all this. We get used to a personalized depth of dimensionality, to our particular nebulous cortège through eternity. (We make the long trek as a *system*, or, more accurately, system of systems, the interactions of which range from the tightly-bound to the somewhat loose.) The onset or realization of significant disease or injury suddenly constrains one's universe—radically, and often irrevocably. These constraints can be physical, as in confinement (hence the benefit of hospital rooms with a view) or

incapacitation. I think from a human point of view, though, our choices of paths through eternity get drastically circumscribed; serious, and perhaps lethal claustrophobia sets in.

Yes, sure, I know that "when one door closes, another opens" sort of thing. But, oh, Monty, we need those alternate doors to choose from. Finding them is not so easy for someone in a somatically, and often mentally attenuated state.

The generalized therapy I have in mind here involves having some kind of, well, not merely advocate, but guide. But the archetype I am looking for is not the learned sorcerer who leaves his inadequately prepared apprentice to stew in his own inundating juices, as it were. The Hermetic docent is closer, though it connotes finality: Traditionally, the psychopomp guided souls to an afterworld, to the far shores of the Styx. For present purposes, I think the best archetype, perhaps, is Janus, the god with the keys (all the better to open doors with), represented with two faces, one looking backward in time, the other toward the future—thus also the god of (new) beginnings.

Portals of Light: *Facing the Grim Weavers of the Shaft*

Again, the goal of ameliorative therapy, as I see it, is not necessarily to extend one's personal future. (After all, some form of disease process is the wind that will make most of us lose our balance on the high wire in the acrobatics routine of life; in this sense, evolutionary adaptations are all about *lineages* and, the "Selfish Gene" enthusiasts notwithstanding, *groups*!) but to point to, and unlock, new doors. Which doors? My friend Sister Claire, a Carmelite nun, speaks of "value" in this context. Value is, of course, a guide to homeostatic action, whether at the scale of a bacterium following a glucose gradient or of a religious martyr adhering to an ethic. This brings us, as humans with a rich ethos, full-circle to joy, happiness, fulfillment, empowerment, service...and love.

Who is to be the guide, this solicitous "janitor" with the key ring? There's the rub, of course. In the "specialist" system that is so much a dynamic of economies nowadays, no one professional can be either an advocate, as previously noted, or a custodian in the sense I mean. Again, it solves nothing to outsource "spiritual guidance", which merely becomes yet another specialty. Yet, the wise and effective clinician *does* become something of a mentor; it can't be all about mechanical fixes (with the double-edged sword the major tool). "Causation" is never that simple, as it is *systems* "all the way down", and surely all the way up as well—systems within systems that are complicity bound.

I am fortunate to have a doctor who seems to feel this more than many, though the dynamics of current medical practices are not helpful. Sometimes, "rant therapy" can assist. As for myself, however, I do not, like Dylan Thomas, "Rage, rage against the dying of the light" (Thomas was, at age 37, very old indeed when his villanelle advised against going "gentle into that good night"), though I will challenge, with as much curmudgeonly vigor as I can muster, the gods at every turn. Deities can be tricky, you know, and need to be kept honest, to have their butts kicked now and then, as they often get matters wrong; even the fates cannot see the warp and weft behind all doors. But the very uncertainty of life is, I believe, a good thing, a brilliant thing. We were born to guess which doors to open, This works well, until it doesn't: We have also known since, well, pretty much since birth that

behind *some* door the ferryman stands, awaiting payment of his *obol*, his toll. Yet, giving over our winnings to this ultimate professional guide is itself an act of homeostasis, of balance, for we are all part of something yet greater that also needs fine tuning. Finally, out thrust through eternity goes ever on.

A. G. Swanson
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