

IDEAS FOR THE FUTURE

The field of dysautonomias could be a prototype for new ideas that will influence the future of medicine. This is because of their complexity, chronicity, and multi-disciplinary, mind-body nature.

In large part I am presenting in this section a kind of philosophy, rather than a textbook discussion of symptoms, signs, tests, or treatments of specific conditions. I'm very curious to learn from you if you agree, by getting in touch with me at goldsteind@ninds.nih.gov.

This section dwells on two implications of this perspective. First is the “mind-body” issue. Dysautonomias involve abnormalities at the border of the mind and body. In evaluating patients with a known or suspected form of dysautonomia, trying to separate the mental from the physical aspects is not helpful, either for diagnosis or for treatment.

Dysautonomias are generally chronic disorders of regulation. They involve many body systems at the same time and are treated with many drugs, which not only can interact with each other but also with other conditions that the patients may have. Dysautonomias can involve functional changes in several feedback loops, where there is no single abnormality at any particular place in the loops but dysfunction of the system as a whole.

The second implication is that some forms of dysautonomia are associated with chronic degenerative conditions such as Parkinson

disease or congestive heart failure, where long-term stress leads eventually to system breakdown by accumulated wear and tear. We are just beginning to understand how genetic predispositions interact with life experiences and time to produce chronic diseases in old age. Scientific integrative medicine is a way of thinking of disorders of regulation of the body's inner world that includes early detection and prevention in the pre-symptomatic phase.

MIND-BODY DISORDERS

Dysautonomias are, possibly more than any other ailments, mind-body disorders.

Dysautonomias are mind-body disorders.

This is a difficult subject for both doctors and patients. The problem is the old notion that the body and mind are separate and distinct in a person, and so diseases must be either physical or mental. If the disorder were physical, it would be “real,” something imposed on the individual, while if it were mental, and “in your head,” it would not be real, but something created in and by the individual.

Distinctions between the “body” and the “mind,” the physical and mental, problems imposed on the individual and those in the mind of the individual, are unhelpful in trying to understand dysautonomias.

These notions date from the teachings of the Renaissance philosopher, Descartes. In my opinion they are outdated by now and inappropriate and unhelpful in trying to understand disorders of the autonomic nervous system.

Here is why. Remember how earlier in this book you learned about



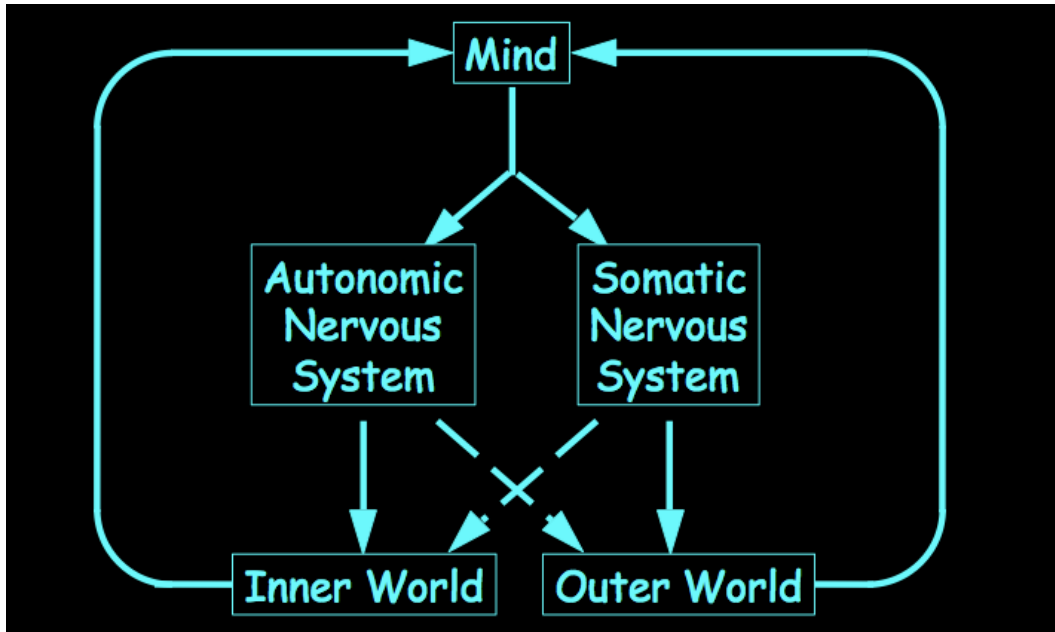
Traditional separation of mental from physical illness.

the “inner world” and the “outer world”? The mind deals with both worlds, simultaneously, continuously, and dynamically in life. Conversely, both worlds affect the mind, and each individual filters and colors perceptions of the inner and outer world. For instance, there is no such thing as a person exercising without “central command,” to tense and relax specific muscles. At the same time, and as part of the same process, the brain automatically directs changes in blood flow to the muscles. The exercising muscle and changes in blood flow lead to information—feedback—to the brain about how things are going both outside and inside the body.

The autonomic nervous system operates exactly at the border of the mind and body. The brain uses and depends on the autonomic nervous system for the internal adjustments that accompany every motion a person performs and every emotion a person feels.

The autonomic nervous system operates at the border of the mind and body.

You already know this, if you think about it. When you jog, for instance, the blood flow to the skin and muscle increases, the heart



A systems approach to the mind-body issue.

pumps more blood, you sweat, and you move more air. These are automatic features of the experience of exercising. Can you imagine exercising and not noticing these things?

It's also true that virtually every emotion a person feels includes changes in the same body functions. For instance, when you are enraged, the blood flow to the skin and muscle increases, the heart pumps more blood, you sweat, and you move more air.

From the point of view of the bodily changes, it would matter little whether these changes resulted from the physical experience of exercise or the mental experience of rage. Both situations involve

alterations in the activity of components of the autonomic nervous system. Both situations involve changes in the inner and outer worlds. And if your autonomic nervous system were to malfunction, your reactions to either situation would not be regulated correctly; in either situation you could feel sick, look sick, and be sick!

A “systems” approach helps to understand dysautonomias. According to the systems approach, the mind simultaneously directs changes in the somatic nervous system and the autonomic nervous system, based on perceptions about what is going on in the inner world and the outer world.

Note that the autonomic nervous system affects both the inner world and outer worlds. For instance, if a person looked pale, because the blood had drained from the face, and were sweaty, trembling, and mumbling incoherently, other people would likely react to these signs of distress and ask, “Are you OK?” And it is well known that strong emotions, probably via adrenaline release, can energize an individual. Recall that one of the entries under weightlifting in the Guinness Book of Records referred to a 123-pound mother who summoned the strength to lift the front end of a car after a jack had collapsed and the car had fallen on her child.

Analogously, the somatic nervous system can affect the inner world via the autonomic nervous system. For instance, you can voluntarily increase your blood pressure any time you want, by clenching a tight fist, or dunking your hand in ice cold water.

How would a systems approach help to understand a dysautonomia? A malfunction at almost any part of the system could lead to alterations in activities of components of the autonomic nervous system. For instance, if there were no feedback to the brain about the state of the blood pressure (part of the inner world), then there would be an inability to keep the blood pressure within bounds, by changing the activity of the sympathetic noradrenergic system. If there were no feedback about the extent of physical exercise, there would also be an inability to adjust the blood pressure and blood flows appropriately. Of course, if there were a failure of the autonomic nervous system itself, this would also interfere with regulation of the inner world, but there would also be difficulty in dealing with the outer world, manifested by problems like exercise intolerance or an inability to tolerate standing for a prolonged period (orthostatic intolerance). Finally, if the person had a psychiatric disorder such as panic/anxiety, then the inappropriate emotional experience of fear would be linked to both autonomic nervous system and somatic nervous system changes.

A clinician's ability to treat a dysautonomia successfully also benefits from a systems approach. Treatments at any of several steps might help, but the best place in the system to insert a treatment would be the step closest to where the cause is—if there is only one.

THE CHANGING FACE OF DISEASE

The Human Genome Project and its descendants have produced a huge fund of information about the normal and diseased human genome. This information is not static but is expanding rapidly, due to identification of single nucleotide polymorphisms, splicing variants, whole gene or nucleotide sequence repetitions, variations in genes encoding transcription factors and promoters, multiple simultaneous genotypic changes, genetic imprinting, mosaicism, and stress and other epigenetic effects on chromosomes. We also are now seeing the introduction of computerized applications to analyze that information.

Even as genetic information-gathering has expanded, the nature of disease has changed. The era of “strep throat medicine” has come to an end. The era of chronic, complex disorders of regulation has begun. These involve derangements of multiple body processes, drug treatments, and interactions among the derangements and the drugs, posing enormous personal and societal burdens. The notion that diseases have simple, single causes that can be cured with a “magic bullet” like penicillin does not apply to dysautonomias or to a large number of other disorders of regulation of the “inner world” inside the body.

For developmental diseases of specific, isolated body processes,

- **Chronic**
- **Degenerative**
- **Complex, multi-system**
- **Long pre-symptomatic phase**
- **Genetic-environmental interplays**
- **Treatment-disease interactions**

The changing face of disease

genotypic or gene expression data might suffice to identify the pathophysiologic pathways from etiology to clinical phenotype in intra-uterine or postnatal development.

Much less clear is how genetic changes already present at birth interact with individual life experiences to lead to multi-system degenerative disorders decades later.

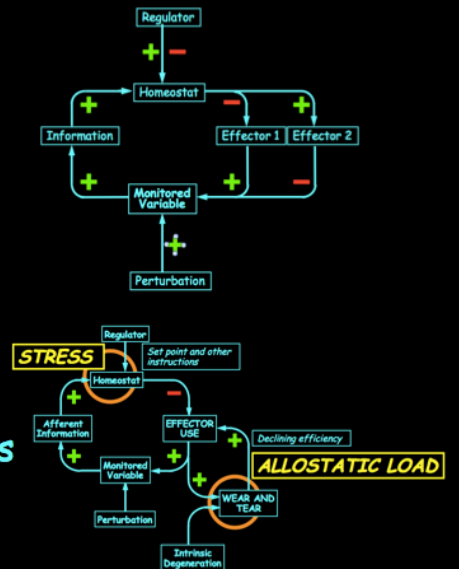
SCIENTIFIC INTEGRATIVE MEDICINE

Scientific integrative medicine is not a discipline, a group of disorders, or a method of treatment, but an approach, a way of thinking. It emphasizes disorders of the multiple interacting systems that regulate the “inner world” of the body. Scientific integrative medicine uses systems concepts to explain diseases in terms of interactions among genetic makeup, life experiences, drug treatments, and time, with the goal of developing strategies to treat, prevent, or palliate multi-system disorders.

Dysautonomias may be a perfect example of how applying concepts of scientific integrative medicine can advance medical science and patient care in the post-genome era.

More generally, concepts of scientific integrate medicine have the potential to forge important links between modern systems biology and classical integrative physiology.

- Negative feedback regulation
- Multiple effectors
- Shared effectors
- Positive feedback
- Homeostatic definition of stress
- Allostatic Load



Key elements of scientific integrative medicine

Linking Systems Biology with Integrative Medicine

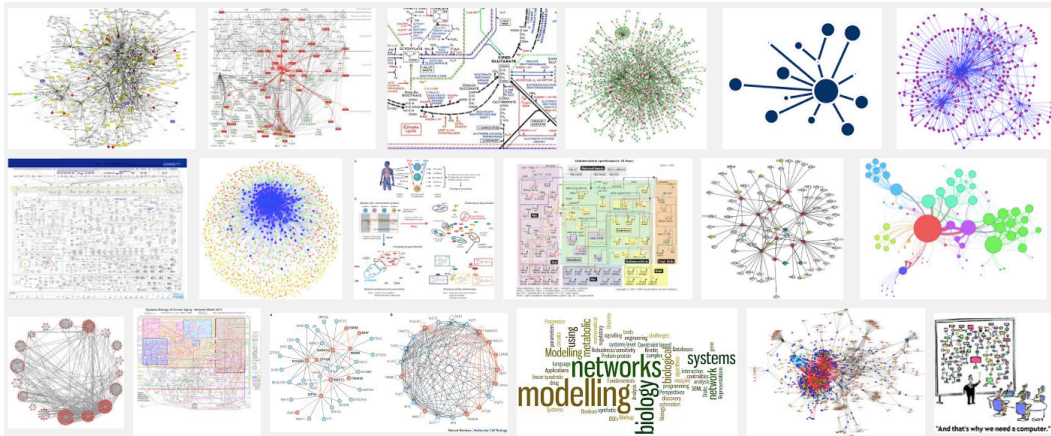
You might at first think that scientific integrative medicine is merely a specialized, applied form of systems biology. Actually, the term, “systems biology,” for which there are now about 5,000 PubMed listings yearly, was rarely used in medical scientific reports before the beginning of the 21st century, whereas the conceptual underpinnings of scientific integrative medicine originated with Claude Bernard in the mid-19th century and Walter B. Cannon in the early 20th century.

Systems biology has been defined variously. One definition is the study of dynamic interactions within biological networks. These interactions can give rise to “emergent” properties unpredicted by any of the components assessed in isolation, and in this sense systems biology can be viewed as “holistic” or “integrative.”

It seems to me that advocates of systems biology have so far not considered sufficiently integrative physiological concepts such as homeostasis, negative feedback-regulated systems, and redundant effectors. Scientific integrative medicine can link systems biology with integrative physiology, because of four distinguishing aspects.

First is the emphasis on regulation via negative feedback loops. This notion follows directly from Bernard’s *milieu intérieur* and Cannon’s homeostasis. Diseases and disorders can be understood in terms of loss of regulation of internal monitored variables because of disruption or declining efficiency at stations in negative feedback loops. Mathematical models incorporating afferent information, homeostats, effectors, etc., can be used to predict the roles of factors such as stress, adaptation, allostatic load, and resilience on the development and manifestations of acute and chronic disorders.

Second, scientific integrative medicine recognizes that in higher organisms the brain dominates in regulation of the body’s inner world.



Systems biology currently focuses on networks in complex webs rather than on hierarchies and negative feedback regulation.

The brain controls levels of many internal monitored variables in parallel—analogue to a computer’s multitasking—each via a homeostatic system. As a corollary, pathophysiologic mechanisms of a variety of complex, mind-body, multi-system disorders involve, and may result from, altered central control.

Third, the brain’s plasticity enables modifications in the step-by-step instructions for organ and systemic processes. According to the concept of allostasis, set-points and other elements of response algorithms vary depending on instinct, imprinting, learning, perceptions, and even simulations of future events by the brain.

Fourth, scientific integrative medicine is medical. Its overall mission

is to understand, rationally treat, retard the progression of, or even prevent disorders and diseases. The systems that maintain the stability of the inner world eventually degenerate, and as their efficiencies decline, the likelihood of deleterious, self-reinforcing positive feedback loops increases, threatening organismic stability and survival. Clinicians manage patients by exploiting negative feedback loops and attempting to forestall or counter positive feedback loops. Moreover, the medications and treatments clinicians prescribe interact with their patients' internal systems. Multiple, simultaneous degenerations, combined with multiple effects of drugs and remedies and myriad interactions among the degenerations and the treatments constitute the bulk of modern medical practice. Scientific integrative medicine offers a schema and vocabulary for approaching the imposing complexity of managing patients.

“Integrative medicine” has also gained cachet recently. The word, “integrative,” has been used synonymously with holistic, complementary, or alternative. The scientific integrative medicine approach, however, actually fits quite well with conventional clinical science and integrative physiology. The emphasis is not on rationalizing or testing the efficacy of holistic or alternative treatment programs but on viewing the body as a coordinated system of systems.

Systems and Regulation of the Inner World

Inside your body is an “inner world,” full of comings and goings and

the beautiful paradox of seeming constancy despite continuous change. We are born, we develop and mature, we reproduce, we live out our lives, we get old, we get sick, and we die, yet for most of our existence we believe in our essential sameness day to day.

For much of our lives we rarely notice the internal workings that constitute the political affairs of the inner world. Things inside seem to stay in a steady state so well, for so long. This applies especially to factors that the autonomic nervous system regulates, such as body temperature, blood levels of key fuels, concentrations of red blood cells in the bloodstream, amounts of electrolytes, the rate of the heartbeat, blood flows to organs, and blood pressure. These and many more “variables” normally don't vary much. Even mood and personality remain about the same.

These steady states do not happen by chance but depend on complex coordination by the brain. The brain regulates the inner world, to maintain apparent constancy despite continual change.

The brain does so via negative feedback systems. For most of our lives we can cling to our belief in sameness because the brain tracks many monitored variables, by way of internal sensory information, and acts on this information to maintain levels of monitored variables at controlled, steady values by modulating numerous effectors that work simultaneously, in parallel.

The foundation of scientific integrative medicine, or systems medicine, is the negative feedback loop.

Scientific integrative medicine finds its roots in the issue of how higher organisms maintain their integrity despite the vicissitudes of life.

The fundamental mechanism is by negative feedback regulation. In response to a change in the level of a monitored variable that is sensed by the brain, the brain directs altered activities of effectors in a manner that tends to bring the level of the monitored variable back to the original level. Components of the autonomic nervous system are key effectors in many of not most of these negative feedback loops.

You have learned that when a monitored variable is regulated by a negative feedback loop, the monitored variable reaches a stable steady-state level and that disruption of a negative feedback loop always increases the variability of the level of the monitored variable. Decreased efficiency of negative feedback regulation of monitored variables of the body's inner world therefore threatens homeostasis.

The situation in heart failure illustrates this phenomenon. As we age, the efficiency of heart muscle function declines—in some sooner than in others, depending on hereditary predispositions and life exposures. As intrinsic heart muscle function declines, the brain senses the decreased pumping ability and directs a compensatory increase in sympathetic noradrenergic system outflow to the heart. This

augments the delivery of norepinephrine to its receptors on heart muscle cells, keeping the cells' contractility and the heart's ejection of blood within normal limits. Bombardment of heart muscle cells by norepinephrine, however, decreases the threshold for the development of abnormal heart rhythms (arrhythmias). When an arrhythmia occurs, the heart instantaneously pumps less blood. The brain directs a further increase in norepinephrine release from nerves in the heart, but this augments further the automaticity of the cells. When segments of heart muscle begin to contract autonomously, rather than synchronously, the heart ceases to function as a pump, and the patient suddenly, often unexpectedly, dies. A goal of scientific integrative medicine is to devise means to detect early or even prevent such a catastrophic positive feedback loop. Even after symptoms of heart failure develop, judicious treatment with drugs that moderate effects of norepinephrine could enhance survival.

In patients with chronic diseases of almost any sort, the inner world breaks down eventually. A key way this happens is by development of positive feedback loops. Positive feedback loops threaten organismic integrity and can lead to rapid decompensation and even death.

Here are some scenarios in which transition from a negative feedback to positive feedback situation is harmful.

— A footballer practicing in full uniform in the heat releases

adrenaline, which constricts skin blood vessels and augments heat production in the body, producing heat exhaustion, which releases more adrenaline, bringing on heat shock.

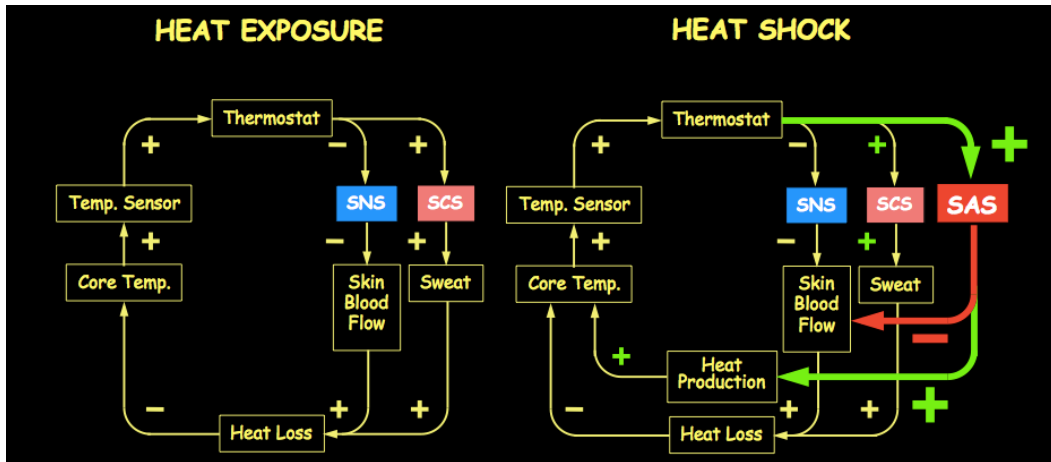
— Heart failure stimulates the sympathetic nervous system and the renin-angiotensin-aldosterone system, which increases fluid retention and growth of heart muscle, worsening the heart failure.

— Chest pain from coronary ischemia due to coronary artery disease evokes distress, stimulating the adrenomedullary hormonal system, increasing the work of the heart and worsening the ischemia.

— Orthostatic hypotension from failure of the sympathetic noradrenergic system causes lightheadedness, a fall, fracture of a hip, and prolonged bed rest in traction, worsening the orthostatic hypotension when the patient tries to get up.

— Loss of dopamine terminals in the nigrostriatal system in the brain increases pathway traffic to the remaining terminals, accelerating dopamine turnover and thereby production of toxic by-products of dopamine metabolism, increasing the rate of loss of dopamine terminals, eventually manifesting clinically as Parkinson disease.

— A viral illness causes dehydration, orthostatic intolerance, and



The transition for heat exposure to heat shock can be explained by initiation of positive feedback loops.

compensatory activation of the sympathetic noradrenergic system, resulting in postural tachycardia syndrome (POTS). Because of ongoing fatigue the patient spends more time in bed, the muscles atrophy, and the blood volume declines, resulting in worsening of orthostatic intolerance and exaggeration of POTS symptoms.

The timing and rapidity of system failure from positive feedback loops depend on dynamic interactions between usage experience of the system and built-in manufacturing and design characteristics. In the body, the occurrence, timing, and rapidity of progression of degenerative diseases depend on interactions between environmental exposures and genetic predispositions. The concepts of allostasis and allostatic load provide a framework for linking stress, distress, and acute and chronic dysautonomias.

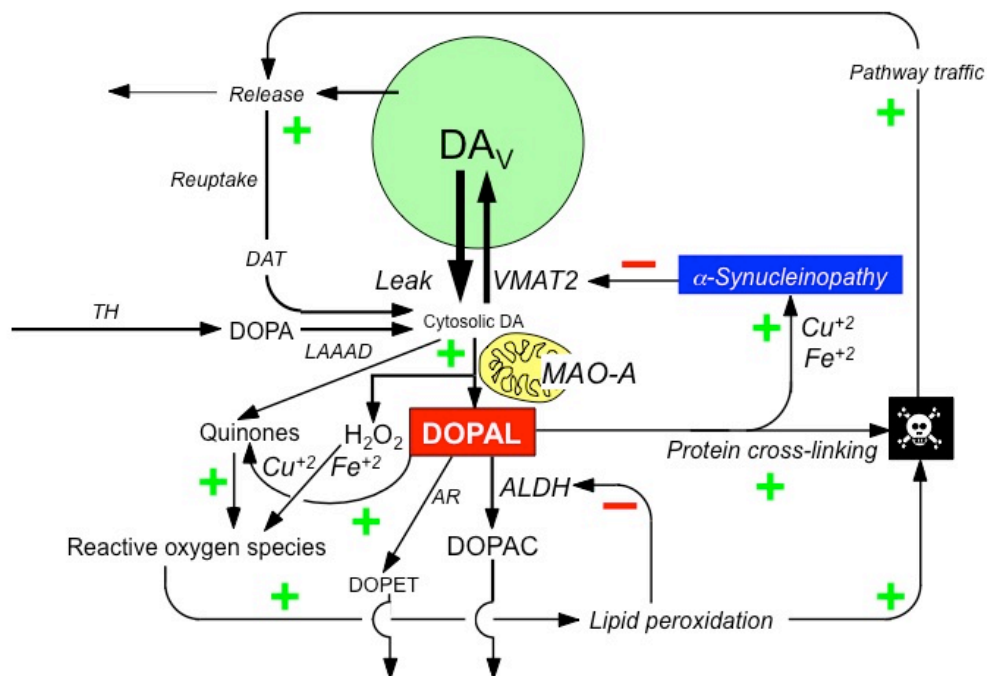
Catecholamine Autotoxicity

Several neurodegenerative diseases involve loss of catecholamine neurons—Parkinson disease is a prototypical example.

Catecholamine neurons are rare in the nervous system, and why they are vulnerable in PD and related disorders has been mysterious.

One explanation, for which evidence is accumulating, is that catecholamine neurons are susceptible *because* they are catecholamine neurons. Catecholamines are “suicide chemicals” that will kill the neuron if they aren’t handled right. By “handled right,” I mean sequestering them in storage vesicles. In the vesicles they are inert, but catecholamines leak from the vesicles into the cytoplasm continuously during life. They are recycled back into the vesicles by the type 2 vesicular monoamine transporter (VMAT2). The remaining catecholamine in the cytoplasm can undergo oxidation, either spontaneous auto-oxidation or enzymatic oxidation catalyzed by monoamine oxidase (MAO) in the outer mitochondrial membrane. The products of both the spontaneous and enzymatic oxidation are potentially toxic.

Accumulating evidence supports the concept of “autotoxicity”—inherent cytotoxicity of catecholamine metabolites in the cells in which they are produced.



Overview of the catecholamine autotoxicity hypothesis

According to the catecholamine autotoxicity theory as applied to the pathogenesis of Parkinson disease, long-term increased build-up of auto-oxidation products and 3,4-dihydroxyphenylacetaldehyde (DOPAL), the catecholaldehyde metabolite of dopamine, causes or contributes to the eventual death of catecholamine neurons.

Lewy bodies, a neuropathologic hallmark of PD, contain precipitated alpha-synuclein. Bases for the tendency of alpha-synuclein to precipitate in the cytoplasm of catecholaminergic neurons have also been mysterious. DOPAL potentially oligomerizes and aggregates

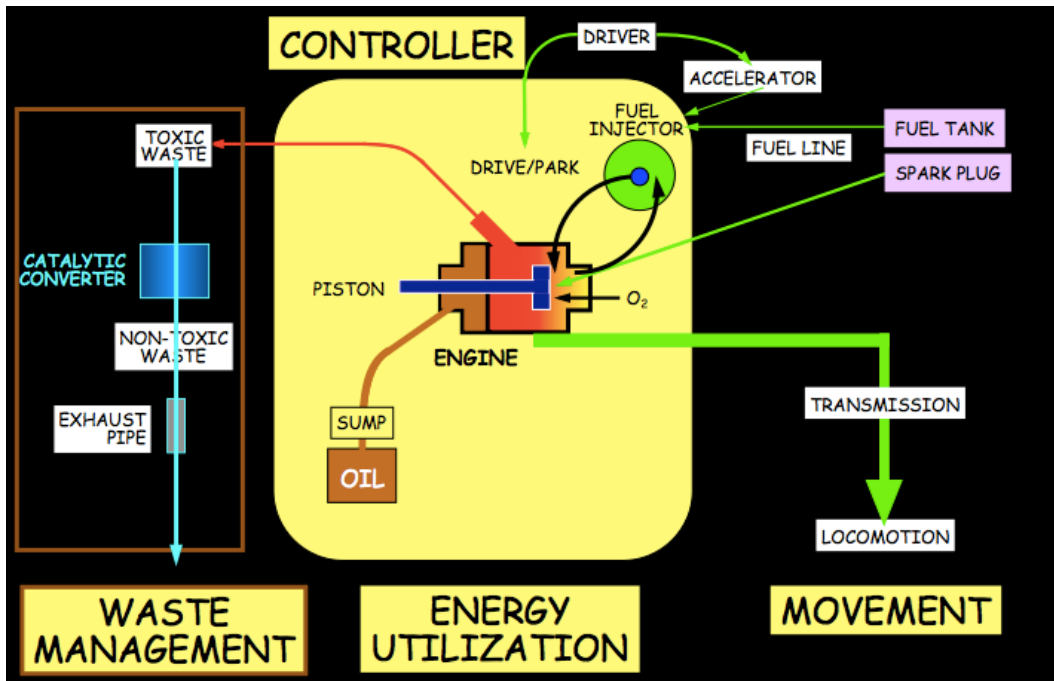
alpha-synuclein. This could be a key link between alpha-synucleinopathy and catecholamine neuron loss in Lewy body diseases.

The concept developed here is that products of catecholamine auto-oxidation, DOPAL, and alpha-synuclein are nodes in a complex nexus of interacting homeostatic systems. Dysfunctions of several processes, including decreased vesicular sequestration of cytoplasmic catecholamines, decreased aldehyde dehydrogenase activity, and oligomerization of alpha-synuclein, lead to conversion from the stability afforded by negative feedback regulation to the instability, degeneration, and system failure caused by induction of positive feedback loops. These dysfunctions result from diverse combinations of genetic predispositions, environmental exposures, stress, and time.

The notion of catecholamine autotoxicity has several implications for treatment, disease modification, and prevention. Conversely, disease modification clinical trials would provide key tests of the autotoxicity theory.

The Getaway Car Analogy

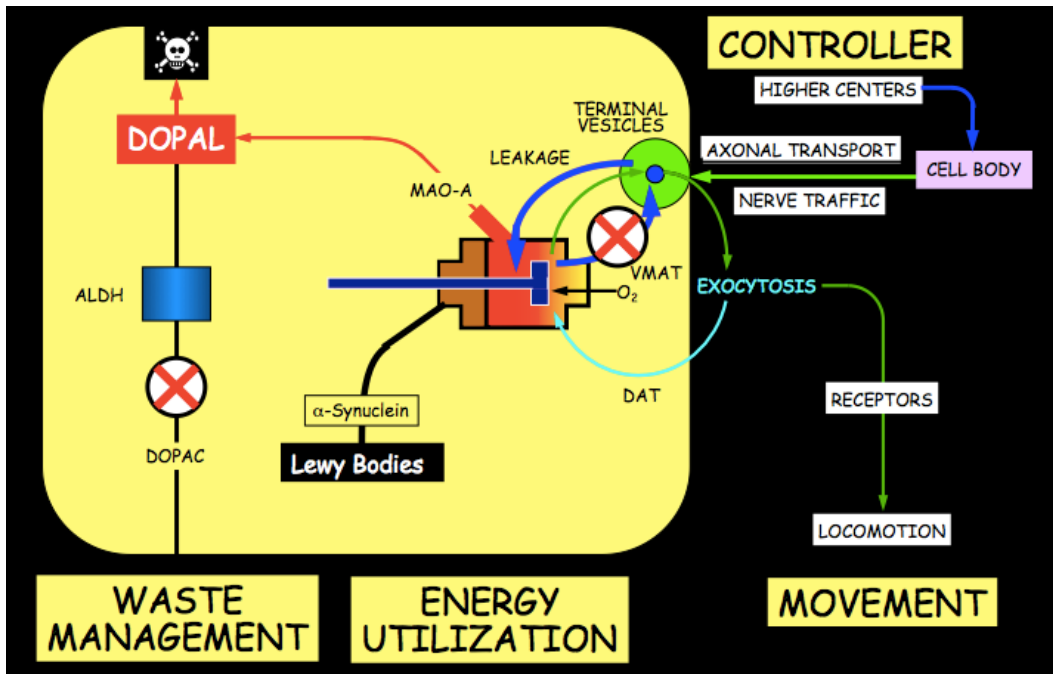
I use the analogy to a bank robber's getaway care to teach about how catecholaldehydes, the products of enzymatic deamination of cytoplasmic catecholamines, can explain the aging-related loss of catecholamine neurons in Parkinson disease and other



Concept diagram for the “getaway car” analogy

neurodegenerative diseases.

The engine of a car converts energy to movement. There is a controller—the driver—that regulates this process. The fuel injector squirts fuel into the combustion chamber, where the fuel is combusted. When the car is idling, the fuel injector squirts the gasoline into the combustion chamber at a slow, continuous rate. Combustion is an oxidative process. The immediate products of the combustion may be harmful, but they are converted to non-toxic



The getaway car analogy used to convey the catecholaldehyde hypothesis

waste products by the catalytic converter, which exit the car via the tailpipe. For the sake of analogy, let's say the amount of fuel in the combustion chamber is limited by recycling back into the fuel injector. The pistons in the engine are lubricated by oil supplied by a reservoir crankcase.

The neurons in an organism convert energy to movement. A complex hierarchy of centers regulate the process, which is coordinated with many adjustments mediated by catecholamines. Under resting

conditions catecholamines in the vesicles leak continuously into the cytoplasm, where they are oxidized spontaneously (auto-oxidation) or enzymatically (by monoamine oxidase-A, or MAO-A). The immediate products of the oxidation are toxic. In particular, 3,4-dihydroxyphenylacetaldehyde (DOPAL) is the toxic aldehyde produced when MAO-A acts on cytoplasmic dopamine (DA). The , harmful byproducts of catecholamine oxidation are to a large extent detoxified by enzymes, the catalytic converters of the neurons. DOPAL is detoxified by aldehyde dehydrogenase (ALDH) converting DOPAL to 3,4-dihydroxyphenylacetic acid (DOPAC). The non-toxic waste products exit the cell. The type 2 vesicular monoamine transporter (VMAT2) recycles the cytoplasmic catecholamines, so that levels of cytoplasmic catecholamines are kept very low. The cytoplasm of the neurons contains a variety of dissolved proteins, including the protein, alpha-synuclein.

What if there were a faulty catalytic converter in the car engine? Then the toxic byproducts of combustion might back up and potentially harm the engine. What if there were deficient recycling of the gasoline back into the fuel injector? Then there would be more production of the toxic byproducts of combustion.

What if there were decreased ALDH activity in a catecholamine neuron? Then DOPAL would tend to accumulate. What if there a vesicular storage defect? Then for a given rate of dopamine synthesis in the cytoplasm, there would be a higher rate of DOPAL production.

If you were a bank robber your getaway car would be kept idling at the curb outside the bank. If the ignition were off, it would take longer for you to get away just when you had to, and if the ignition happened to fail at that crucial time, that would be the end of your career as a bank robber. Suppose you decided not to rob the bank on that particular day and decided to “case the joint.” The car would be kept idling. After several months of reconnaissance and many fuel refills, just from the wear and tear of having had the car in idle all that time, the engine’s life span probably would be shortened because of a buildup of harmful deposits—gunk—inside. The engine might fail completely.

If you did a “post-mortem” on the engine and crankcase, you would find gunk deposits. No amount of analysis of the gunk would pinpoint the root cause of the engine failure. Maybe the catalytic converter had a design or manufacturing flaw, or something interfered with the fuel injector recycling the non-combusted fuel, or the oil had the wrong viscosity, or the driver habitually “floored” the accelerator. You wouldn’t be able to tell.

Even if none of these factors alone would have ever caused a problem in the normal life span of the car, together they could have built up sufficient gunk to kill the engine. Despite the extraordinarily complex design and manufacture of the car, and its obvious importance for you, you might well decide to tow it to the junkyard and sell it for scrap. Nevertheless, you could still decide in the end that it had been

worthwhile to keep that car idling at the curb.

Catecholamine neurons are like the engine in a getaway car. They are “on” continuously, in the sense that dopamine is being synthesized in the cytoplasm, and dopamine and norepinephrine (which is synthesized in the vesicles from dopamine taken up from the cytoplasm) are always leaking from the vesicles into the cytoplasm. Some of the cytoplasmic dopamine that escapes vesicular uptake auto-oxidizes to dopamine quinone, which is then converted to 5-S-cysteinyl-dopamine, dopaminechrome, or 5,6-dihydroxyindole, all of which are toxic. Most of the cytoplasmic dopamine that escapes vesicular uptake is oxidized enzymatically to form DOPAL and hydrogen peroxide, both of which are toxic. If there were a deficiency of ALDH, DOPAL would build up, and if there were a vesicular storage defect, then for a given rate of dopamine synthesis the rate of DOPAL production would be increased.

What about the “gunk”? DOPAL potently oligomerizes and aggregates alpha-synuclein. Lewy bodies, the pathologic hallmark of Parkinson disease, contain abundant precipitated alpha-synuclein.

The high rate of leakage of catecholamines from vesicles into the cytoplasm, and the high rate of reuptake back into the vesicles by way of VMAT2, would at first seem like a waste of energy. What good could this do, as opposed to having a stable pool in vesicles that don't leak? My colleague at the NIH for many years, Graeme Eisenhofer,

came up with an insightful explanation, which he calls “gearing down.” If there were a stable pool of vesicles, then an emergency requiring sustained norepinephrine release would rapidly dissipate that pool. It would be impossible for synthesis of norepinephrine from scratch (the rate of which can only about double) to keep up with the irreversible loss of norepinephrine from the tissue (the rate of which can go up many-fold). But if there were continuous leakage of norepinephrine from the vesicles, and continuous replacement of the norepinephrine by ongoing synthesis, then the organism could maintain a high rate of release of norepinephrine for a much longer time.

Randolph M. Nesse and George C. Williams, in their thought-provoking book, *Why We Get Sick*, asked, “If senescence so devastates our fitness, why hasn’t natural selection eliminated it?” Williams provided an answer in 1957 in his pleiotropic theory, according to which genes causing senescence have early benefits. In lay terms, “senescence is the price we pay for vigor in youth.” Due to the pleiotropic effect of improved resilience and anti-fatigue at the cost of autotoxicity, accumulation of allostatic load in catecholaminergic neurons may lead eventually to multiple positive feedback loops and to the loss of those neurons in neurodegenerative disease such as Parkinson’s disease.

The catecholaldehyde hypothesis and getaway car analogy lead straightforwardly to testable ideas about how to delay the onset of or

slow the rate of aging-related loss of catecholamine neurons. First, inhibit MAO-A, since this would decrease formation of the toxic metabolite, DOPAL. Second, treat with an anti-oxidant, since this would attenuate spontaneous oxidation of cytoplasmic catecholamines. Third, treat with a chelator of divalent metal cations, since divalent metal cations enhance DOPAL-induced oligomerization of alpha-synuclein. Fourth, treat with an aldehyde scavenger, since this would decrease DOPAL levels. Fifth, decrease neuronal catecholamine turnover, by decreasing activity of tyrosine hydroxylase, the rate-limiting enzyme in dopamine biosynthesis, and by decreasing stress-related bursts of catecholamine release, since this would minimize cytoplasmic catecholamine levels.

THE FUTURE IS NOW

Arnold Rice Rich, the Baxley Professor of Pathology and Pathologist-in-Chief at the Johns Hopkins Hospital, was notorious for his biting remarks. Ivan Bennett, who succeeded Rich as Baxley Professor, was at the receiving end of one of Rich's most famous incisive comments. Robert H. Heptinstall (Pathology Chair when I was a medical student at Hopkins in the early 1970s) related the following story. When Bennett had been the head of the infectious disease division of the Department of Medicine, Bennett had received a large Federal grant to build and equip a new research laboratory. Bennett proudly escorted Rich around the splendid, superbly equipped new facility and asked Rich what he thought of it. According to the story, Rich responded, "You know Bennett, I'd trade it all for one good idea."

My "big idea" has three parts: (a) link systems biology with integrative physiology; (b) study patients with multi-system disorders of regulation—specifically, patients with dysautonomias; (c) "flip the clinic," using management of dysautonomia patients as a precedent.

(a) The first part is to link systems biology with integrative physiology. Clinicians often deal with diseases involving complex systems. It is time to develop and apply concepts that take into account the complex pathogenesis of diseases. "Systems biology" as it exists currently has key gaps. One is the lack of inclusion of

negative feedback regulation and multiple effectors. Negative feedback regulation maintains levels of monitored variables within pre-specified ranges. Multiple effectors, in concert with negative feedback regulation, enable compensatory activation of alternative effectors and patterned responses to stressors. Another gap is the lack of inclusion of destabilizing positive feedback loops that result in clinical manifestations and progression of diseases. Finally, medical genetics, because of the ability to identify “first causes” of disease, has resulted in a kind of intellectual leap-frogging from the clinic to the genome, leaving the pathogenetic trail from genome to clinic less well explored.

(b) A corollary of these gaps is that multi-system disorders of regulation remain poorly understood. It is time to pay more scientific attention to disorders of regulation, as these disorders are an increasing public health burden. There are many—obesity (with consequent hypertension, diabetes, atherosclerosis, and stroke), autoimmunity (with consequent multiple allergies, multiple sclerosis, etc.), dysregulation of central neurotransmitters (with consequent depression, panic/anxiety, and cognitive dysfunction), neuropathic pain, and dysautonomias. These topics all have important nervous system facets; one might even take the extreme position that they all ultimately are neurological disorders, because of the dominance of the brain in maintaining the “inner world” of the body.



“I have Parkinsons.”
Are you at risk for PD?
Please visit the website of the
NIH (NINDS) PDRisk
research study at:
<https://pdrisk.ninds.nih.gov>



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Future medical research and practice will be heavily based on the internet.

(c) Third, it is time to “flip the clinic.” Patients with multi-system disorders of regulation should have more power and responsibility to manage their own health. This could be done intelligently with the active participation of patient support groups but will require novel approaches to practice, education, and research via the internet.

Flipping the Clinic

The term, “flip the clinic,” refers to an initiative by the Robert Wood Johnson Foundation (RWJF). RWJF considers this to be less a full-fledged program than a “conversation” in progress.

Flipping the clinic is an attempt to achieve two key goals. The first goal is to empower patients, family, and caregivers to be more informed and engaged in their own health and health care. The second goal is to enable healthcare providers to improve the ways they communicate with patients and support them better during and between office visits.

I hope this textbook is a step in “flipping the clinic” in the areas of autonomic and systems medicine.

The notion of flipping the clinic draws inspiration from Sal Khan, founder of the Khan Academy, the well-known not-for-profit organization that aims to offer “free world-class education” online, through an extensive library of videos and lectures as well as interactive challenges and assessments. As such, Khan Academy has sought to “flip” the classroom; instead of listening to lectures in the classroom and doing “homework” at home, students listen to lectures at home and do “homework” in class, where the teacher can help students who are having difficulty. Students can also proceed at their own pace, mastering the material on their own schedule, not the teacher’s or the classroom’s.

From a scientific point of view, flipping the clinic will be especially valuable for patients with multi-system disorders of regulation, such as dysautonomias. A system of education, lifestyle adjustments,

- **Goals**
Power & responsibility of patients
Educate physicians & researchers
- **Internet-based medical education system**
- **Internet-based autonomic medical care system**
- **Dysautonomias as a prototype**
Applicable to other disorders of regulation

Ideas about “flipping the clinic” in the field of autonomic medicine

support groups, and internet-based outcomes research can be compared with the standard medical practice models, in terms of both cost-efficiency and patient satisfaction.

Flipping the clinic applies similar principles to medical practice. I envision an internet-based, mutually educational system that is accessible by patients, students, and practitioners. This textbook is a step in that direction.