FROM MY PERSPECTIVE

LITERATURE-RELATED DISCOVERY AND INNOVATION - UPDATE

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ABSTRACT

Literature-Related Discovery and Innovation (LRDI - formerly LRD-Literature-Related Discovery) integrates 1) discovery generation from disparate literatures with 2) the wealth of knowledge contained in prior art to 3) potentially reverse chronic and infectious diseases and/or 4) potentially solve technical problems that appear intractable. This article describes the evolution of LRDI by the author and the insights gained/lessons learned over the past decade. To illustrate the potential power of LRDI, the article emphasizes the relationship between the results of our 2008 LRDI multiple sclerosis (MS) study and a recent demonstration of MS reversal.

Lessons learned from the six LRDI medical studies done so far include:

*The main operational problem in the author's LRDI approach is selecting the most important concepts from extremely large volumes of potential discovery retrieval. This is contrary to most published LRDI research, where the discovery focus is searching for rare events.

*It is important to have topical specialist(s) working closely with information technologist(s); the topical specialist(s) applies judgment in selecting the most important concepts.

*A functional form of the information retrieval query with proximity searching capability provides highly selective filtering for discovery retrieval and core prevention/treatment retrieval; the functional form of the query with proximity searching capability allows use of full-text for discovery and core prevention/treatment.

*Bibliographic coupling (identifying papers that share common references) combined with text-based relationships strengthens selection for potential discovery further.

*Having 'skin-in-the-game' (being affected personally) relative to the medical outcome is a strong incentive to do whatever is necessary to solve the research problem.

*Hormesis is critical to healing; relatively modest doses of stimuli tend to be beneficial, whereas relatively large doses may be harmful. The synergy of hormetic treatment doses produces effects larger than combinations of individual doses and requires smaller doses when combined; the synergy of hormetic doses allows conversion of

megadoses of nutrients typically reported in lab/clinical studies to physiological (food-level) doses and associated increased safety.

*Co-promoters (combinations of toxic stimuli required to produce disease symptoms) are extremely important for explaining seemingly conflicting results; if true co-promotion is present, elimination of one of the co-promoters may be adequate for removing symptoms, even though the overall problem persists.

* Prior art (potential treatments already published in the literature but not pursued by mainline medicine) may have much to contribute to potentially solve many serious medical problems; much of prior art is overlooked, especially low-tech prior art (e.g., foods, food extracts, herbs, etc).

*Systemic and focused treatments are both necessary components of healing, but neither will be fully, or many times even partially, effective until the cause(s) is identified and removed. Any medical approach that involves administering treatments for chronic and infectious diseases without addressing the cause(s) results in a broad range of outcomes mainly involving substitution of one set of symptoms for another.

*Past results of LRDI medical studies showed much overlap among preventatives/systemic treatments for different diseases. Differences will arise mainly in focused treatments, especially those involving high technology.

*The central parameters to healing in much medical research are never identified nor reported. Many treatments require a combination of skilled practitioners, cause removal, and immune/neural/endocrine/circulatory systems to be healthy for full effectiveness, yet practitioner skill, degree of cause removal, and immune system et al health are never reported. Lack of this information does not allow efficacy of different treatments to be compared. Reviews and meta-analyses that compare and draw conclusions about the effectiveness of these different treatments without the above critical information being reported are of extremely limited value and credibility.

*Finally, the most important deficiency for fully reversing chronic and infectious diseases, as well as rapidly accelerating healing of injuries and wounds, is the credibility and integrity of the medical literature itself, especially in areas that concern commercial and government/political sensitivities. In the evaluation of many concepts that deviated from the norm, it was difficult to ascertain whether the difference was based on solid high-quality research, poor research, or deliberately skewed research.

KEYWORDS

Literature-Related Discovery; Literature-Related Discovery and Innovation; Text Mining; Multiple Sclerosis; Discovery; Innovation; Disease Prevention; Disease Treatment

DEFINITIONS

Literature-related discovery (LRD) is a systematic approach to bridging unconnected disciplines based on text mining procedures. LRD allows potentially radical discovery to be hypothesized using either the technical literature alone, or the literature and its authors (e.g., adding workshops, panels, etc to the literature analysis). In the LRD context, discovery is linking two or more literature concepts that have heretofore not been linked (i.e., disjoint concepts), in order to produce novel, interesting, plausible, and intelligible knowledge. Literature-Related Discovery and Innovation (LRDI), the most recent incarnation of LRD, integrates discovery with innovation (re-invigorating prior art, specifically) to solve problems of interest.

PURPOSE OF ARTICLE

In 2008-9, our research group published 1) a detailed review of the complete LRDI literature in ARIST [1], 2) a journal Special Issue devoted to the LRDI methodology and applications circa 2007 [2-9], and 3) a comprehensive report that covered all the studies in the journal Special Issue and some raw data as well [10]. In 2011, I published an LRDI study on the SARS pandemic/coronavirus [11]. Due to significant advances made in our LRDI technique, and significant insights gained from the past and present LRDI studies, I was requested to provide an update of the technique and key findings. This article describes the development of our LRDI approach, insights gained during the development, and the power of the technique to identify potential preventatives/ treatments for serious illnesses. It provides an example of this power based on recent developments in the reversal of multiple sclerosis (MS).

LRDI OVERVIEW

LRDI has two components: Literature-Based Discovery and Innovation (LBDI) and Literature-Assisted Discovery and Innovation (LADI). LBDI involves mainly analysis of the literature, whereas LADI exploits the knowledge of published authors in an interactive mode (e.g., convening workshops or panels, and brainstorming ideas, using authors identified by literature analysis). Either approach can be open discovery system (ODS), where a problem is specified and the goal is to find solutions, or closed discovery system (CDS), where e.g. a problem and solution are specified, and it is desired to identify the mechanisms by which the solution addresses the problem. LBDI first surfaced as LBD in Swanson's 1986 pioneering paper [12] on potential treatments for Raynaud's Phenomenon (RP).

The general theory behind Swanson's ODS LBD approach, applied to two separate literatures, is based upon the following considerations [12].

Assume that two disjoint literatures can be generated, the first literature AB having a central theme "A" and sub-themes "B," and the second literature BC having a central theme(s) "B" and sub-themes "C." Further assume that linkages can be generated through the "B" themes that connect both literatures (e.g., AB-->BC). Those linkages that connect the disjoint components of the two literatures (e.g., the components of AB and BC whose intersection is zero) are candidates for discovery, since the disjoint themes "C" identified in literature BC could not have been obtained from reading literature AB alone.

IMPORTANCE OF LRDI TECHNIQUE

Before proceeding to the development history and upgrades for LRDI, the potential value of LRDI will be described. Why is LRDI important? What has it demonstrated so far, and what is its potential? One example will suffice.

Reversal of MS

I recently came across a paper [13], a book [14], and a video [15] describing the reversal of MS for one patient (an M.D. on the medical faculty of the University of Iowa, Dr. Terry Wahls). To my knowledge, it is the first documented complete reversal of MS. The main component of the treatment the author/patient recommended was a strict diet. Its major components included greens [kale, parsley, etc]; sulfur-rich vegetables [cabbage, broccoli, etc]; flavonoids/polyphenols [berries, strongly-colored vegetables and fruits, etc]; omega-3 fatty acids [wild salmon, herring, etc]; grass-fed meat [organ meats, etc]; seaweed). The author/patient eventually added neuromuscular electrical stimulation (NMES) to both grow new muscle and re-activate existing muscle, thereby reversing the damage from MS. Prior to the implementation of the strictest version of the diet, her progress with NMES was very slow. Once the final diet was used, progress increased rapidly.

LRDI Study on MS

In 2007, our research group at the Office of Naval Research conducted an LRDI study of potential preventatives/treatments for MS [7]. While the emphasis was on potential discovery, we also identified potential treatments/preventatives from the core MS literature (defined as the intersection of "multiple sclerosis" with various

non-drug substances (mainly foods/food extracts) and lifestyle modifications), and listed some of them in Appendix 9 of a comprehensive report on all our LRDI studies circa 2007 [10].

After reviewing the paper [13], book [14], and video [15] describing the MS reversal, I re-examined the core MS literature at the time of our study. From Abstracts and titles only, the following are some of the potential causes/contributory factors and potential treatments I identified.

-Potential causes: high latitudes/lack of sunshine/Vitamin D deficiency; excess total fat, especially animal fat; smoking; polyunsaturated fatty acid deficiency; B-vitamin deficiency; milk consumption; excessive hard liquor consumption; excessive coffee consumption; solvent exposure; ionizing radiation; smoked meat; pork/hot dogs; allergenic foods; sugar/sweets/candy; mercury; excessive advanced glycation end products (AGEs), others.

-Potential treatments:

--Reduce or eliminate smoking, allergenic foods, excessive alcohol consumption, excessive coffee consumption, sugar, total fat consumption, milk consumption, ionizing radiation exposure, solvent exposure, mercury exposure, AGEs (reduce food processing temperatures), others.

--Add (general description) dietary antioxidants, thiol antioxidants, adaptogenic phytonutrients, probiotics, fresh fruits, vegetables, dietary fiber, flavonoids, n-3 polyunsaturated fatty acids, essential minerals, caloric restriction, fish, vitamin-B, Vitamin D; sunshine, dietary polyphenols (phenolic acids, flavonoids), whole foods, others.

--Add (specific description) coQ10, potassium, calcium, cod-liver oil; alpha lipoic acid (ALA)/docosahexaenoic acid (DHA)/; green tea, salmon, curcumin, linoleic acid, luteolin, , quercetin, Vitamin C, folate, B6, B12, thiamine, riboflavin, evening primrose oil, acetyl L-carnitine, glycerophosphocholine, phosphatidylserine, iodine, others.

To provide one example of what is subsumed under some of the general recommendations for addition to the diet, consider the dietary/thiol antioxidant category. It consists of items like Carotenoids (e.g., carrots, peppers, tomatoes, leafy greens like kale, collards and spinach, citrus fruits, etc), Flavonoids (e.g., anthocyanins [cherries, grapes and berries], flavanols [dark chocolate, ginko biloba], proanthocyanins [red wine/ grapes/ resveratrol], apples, broccoli, citrus, cinnamon, and some teas), Isothiocyanates (e.g., cruciferous vegetables [broccoli, cauliflower, kale, cabbage and horseradish], Sulfides/ Thiols (e.g., cruciferous vegetables, garlic, onions, leeks, scallions and bok choy),

Phenols (e.g., apples, pears, citrus fruits and some vegetables), Phenolic Acids (e.g., coffee, wine, pomegranate, blueberries, cranberries, lingonberries, green tea, onions and kale).

LRDI Study and Reversal of MS

What is the relationship between the above potential treatments identified in our core MS literature and the recommended diet in Dr. Wahls' paper [13], book [14], and video [15]? The above list of potential treatments has three components: 1) reduce or eliminate the suspected causes; 2) add members of a general class of nutrients, and 3) add specific nutrients identified. If we focus solely on the nutrients to be added, there are hundreds if not thousands of specific items that could be integrated to form a recommended diet. A real-world diet would consist of perhaps a few tens of these items. Thus, the number of potential combinations of ten-twenty foods/food extracts that could be generated from the above list of hundreds of candidates is astronomical. How do we translate from this large list of candidates to a reasonable number for a diet?

A computer-based approach examining all combinations would not be adequate, even if a sufficiently large computer were available. There may be synergies associated with each combination that would add to/detract from the value of the individual components of each combination together, and most, if not all, of these synergies would not be known without lab tests/clinical trials. Thus, another approach is required.

In the MS LRDI study [7], we identified major biomedical problems/roadblocks that needed to be addressed/overcome in order for healing to occur. One six-factor taxonomy we developed [7], based on the published papers in the prior art MS literature, was the following (where the phrases in parentheses are key biomedical thrust areas within each factor):

Factor 1: Myelin sheath proteins and maintenance cells (myelin basic protein*; myelin oligodendrocyte glycoprotein*; proteolipid protein*; experimental autoimmune encephalomyelitis; oligodendrocyte*; encephalitogenic; epitope*; immunization; immunodominant)
Factor 2: Indirect contribution of lymphocytes to inflammation by secretion of cytokines, chemokines, and lymphokines (cytokine*; tumor necrosis factor-alpha; peripheral blood mononuclear cells; interferon-gamma; proinflammatory; interleukin*)
Factor 3: Viral contributions to inflammation (murine encephalomyelitis virus; virus; viral; demyelinating)

Factor 4: Autoimmunity (cerebrospinal fluid; oligoclonal IgG bands; isoelectric focusing; glial fibrillary acidic protein; Intrathecal IgG; IgG index; immunofixation; electrophoresis)
Factor 5: Demyelination and remyelination (oligodendrocyte*; demyelinat; glial fibrillary acidic protein; astrocyte*; axon*; myelin oligodendrocyte glycoprotein*; remyelinat*)
Factor 6: Blood–brain barrier (vascular cell adhesion molecule-1; intercellular adhesion; ICAM-1; endothelial; endothelial cell*; cell adhesion molecule*; endothelium).

A straight-forward approach to translating from the wide range of nutrients available to a feasible diet contains two components: use whole food/low temperature processing (if necessary) implementation of the general and specific treatment candidates above, and insure that the total recommended diet addresses each of the six factors above. We have emphasized whole food implementation of the nutrient findings in all of our LRDI studies. The biomedical literature has shown that there are substantive synergies to be realized when the constituents of a food are taken together relative to their benefits when taken in isolation. Additionally, there are synergies to be realized when groups of beneficial whole foods are taken together. Finally, the hormetic (beneficial) doses of nutrients when combined in whole food synergies are lower than when these nutrients are provided in isolation, and megadoses that seem to be required in lab tests and clinical trials of isolated substances translate into physiological doses (food portions) when provided in synergistic combination.

When the two-component approach is used, one of the diets that results is the one recommended by Dr. Wahls above (*with the possible exception of meat; I did not see a strong case for meat relative to the other items in the medical literature*). Obviously, other diet options are possible, and they could theoretically work as well as, or better than, Dr. Wahls' recommended diet. It should be noted that, while Dr. Wahls' documented accomplishments in this area are impressive and ground-breaking, at the present time they are for one person, with one set (among many) of potential MS causes, in one geographical region, one culture, one ethnicity, etc, etc. Even the limited information we found in the core MS literature in 2007 covers a wide variety of potential causes, and has a broader variety of potential treatments than Dr. Wahls' recommendations. Most of these potential causes and treatments have been in the literature for a decade or longer.

And, this discussion has been limited strictly to the core MS literature. Much more was obtained from the core related literatures, both in prior art ('prior art' in the present context refers to the 'disease' and the 'treatment'

occurring in the same article) and potential discovery. For a prior art example in the related literatures, one problem area to be addressed dealt with mitochondria, characterized by key words such as mitochondrial dysfunction, mitochondrial swelling, mitochondrial insufficiency, etc [7]. Using the preceding three phrases as search terms, I re-examined a small portion of the 2007 literature for prior art in this area, and it included items like co-supplementation of carnitine and lipoic acid, reduce dietary fat, add selenium, caloric restriction, exercise, avoid aluminum, add acetyl-l-carnitine, etc. These records made no mention of MS, yet, the recommendations and findings strongly overlapped those in the core MS literature. This suggests a strong association between mitochondrial dysfunction, mitochondrial swelling, mitochondrial insufficiency and MS.

The bottom line is that diets equivalent to Dr. Wahls' or perhaps even better could have been obtained from our 2007 core MS literature findings, with additional potential benefits from the potential discovery findings. Our findings could identify other potential causes of MS to be eliminated as well. In our latest incarnation of LRDI, we are identifying every potential cause 1) from the problem literature, 2) from related literatures that may be extrapolated to solve the problem of interest, and 3) from hypothesized causes based on fundamental biological mechanisms. We have removed all restrictions on potential treatments, which, combined with identifying all potential causes, will provide the most comprehensive disease reversal options possible.

In the 2007 MS LRDI study [7], we concluded the following: "The picture from the handful of potential discoveries reported in this paper (and the hundreds of additional potential discoveries possible with a properly resourced study) is a synergy of lifestyle/dietary practices that could be interpreted as anti-MS. Along with non-discovery items such as Vitamin D, dietary chelators, caloric restriction, complement-inhibitory herbs, Nigella sativa oil, green tea, and quercetin are potential discovery items such as Shogaol, Ethanol, Iron, Petaslignolide A, Mangifera indica L, Tiliroside, Gnaphaliin, Cissus quadrangularis extract, Kalpaamruthaa, Salvia miltiorrhiza Bunge, Inchinko TJ-135, Silymarin, Edaravone, Sopoongsan, and Artemesia iwayomogi."

In the 2007 PD (Parkinson disease) LRDI study [6], we concluded the following: " The picture from the handful of potential discoveries reported in this paper (and the hundreds of additional potential discoveries possible with a properly resourced study, including additional semantic classes such as Environmental) is a synergy of lifestyle/ dietary practices that could be interpreted as anti-Parkinson. Along with non-discovery items such as less dairy,

green tea, caloric restriction, blueberries, broccoli/broccoli sprouts, and lower temperature cooking are potential discovery items such as malanga extracts, kolaviron, isohumulones, brown algae, and Rhododendrum flavonoids. "

While our conclusions included some of the items in Dr. Wahls' recommended diet and our findings above from the MS core literature, we did not provide the type and level of detail of recommended diet that we have shown above. Why didn't we recommend these types of diets shown above in 2007 for MS and the other diseases we studied?

We basically underestimated the value of the prior art contained in the medical literature, and the powerful capability of diet as a major factor to reverse serious diseases. Like most members of the general population, and the medical research and clinical community as well, we followed the standard paradigm that exotic treatments or 'magic bullets' were necessary to 'conquer' these serious diseases. After all, hadn't billions of dollars in research funds and clinical trials been spent over the years in fruitless attempts to find 'cures' and effective 'treatments' for the most serious diseases? If relatively simple and straight-forward approaches were possible for these diseases, why would all that money have been spent on the exotic and high-technology?

We thought that esoteric discoveries were required to identify these 'magic bullets', and many of our published potential discovery examples focused on the esoteric foods and food derivatives, although (as shown in the quoted text above) we did include examples of the benefits of fresh fruits and vegetables, caloric restriction, low temperature food processing, etc. As Dr. Wahls' results have shown, we can now ask why healing for these serious diseases should be focused so heavily on the complex and esoteric, at least for most patients? This narrow focus on complexity occurs when causes are not pursued or deliberately concealed, and 'treatments' are provided having little to do with addressing causes. The heavy focus on complexity for disease reversal occurs in many cases because complexity is profitable. That is not to say all these serious diseases are 'curable', or that complexity is never required. Once Dr. Wahls reversed MS, the advanced technology of NMES was required to ***reverse the damage from MS***. In other words, the simple approach was adequate to reverse the ***disease of MS***, and complexity was required to reverse the ***damage from MS***.

However, there is an equally compelling real-world issue for our not having provided detailed (mainly dietary) treatment recommendations in the absence of proof-of-principle demonstrations. Had we proposed a recommended diet or groups of diets (as shown above) in 2007 without demonstration that it/they worked, who would have

followed it? Had Dr. Wahls proposed her recommended diet in 2007 without demonstration that it worked, who would have followed it? It's difficult enough to convince people to change their behaviors and eating habits when hard data is available. Twenty-one percent of adults still smoke, half the number that smoked when the Surgeon General's Report on smoking was issued 48 years ago. This 50% reduction follows strong consensus within the scientific community on the harmful effects of smoking, and the imposition of countless additional taxes on smoking and many no-smoking mandates. Most people have become heavy users of cell phones and WiFi, despite increasing evidence that serious harm can occur, especially for children [16]. Most people would have regarded such diet recommendations in 2007 as just another list to ignore.

Importance of Strict Diet or other Cause Removal for Reducing Co-Promoter Effects

Dr. Wahls has shown that, for at least one data point, following a strict dietary regimen can have powerful healing effects. Even in those cases where co-promoters exist (e.g., poor diet, ionizing radiation, non-ionizing radiation), many times each co-promoter by itself may not be strong enough to cause symptoms, and in those sub-sets where diet is such a co-promoter, improving the diet alone may be adequate to eliminate symptoms. Additionally, if poor diet is a major factor in disease progression, auxiliary treatments to accelerate healing may show little effect under poor diet conditions. If diet is improved and removed as a cause, this may allow auxiliary treatments to accelerate healing substantially.

Importance of Strict Diet or other Cause Removal for Enhancing Treatments

Dr. Wahls eventually integrated nutritional enhancement with NMES. Her experience was that she used NMES and made very slow progress, then improved her diet and made rapid progress. This comports with the LRDI approach, one thesis of which states that ***unless the cause(s) is removed, treatment will be ineffective***. This appears to be exactly what happened in Dr. Wahls' case; the cause (poor diet) was removed and the treatment (NMES) became effective.

If one separates the sequence of events necessary for healing into 1) disease cause removal, 2) disease symptom removal, and 3) disease damage removal, explanation becomes somewhat easier. Dr. Wahls eliminated the major ***cause*** of her MS (poor diet), and the ***symptoms*** associated with MS disappeared (pain, fatigue, etc). However, the ***damage*** from MS (gait and motor control problems) remained, to some extent. To reverse that damage, she had two

major options. She could let nature take its course and reverse the symptoms of the damage. This alone might work, but natural biological processes can take a long time for healing. For faster results, she could use some external form of treatment to accelerate healing. She chose NMES, and, in combination with improved nutrition, was able to accelerate healing.

Now comes one of the more critical findings of this paper. If we rate the quality of diets from one to a hundred, where one is the lowest, then, assuming Dr. Wahls had an average American diet before she contracted MS, her diet pre-2000 (before being diagnosed with MS) was perhaps a 40. Then, she was diagnosed with MS, started to deteriorate, and changed to a Paleolithic diet (there are various incarnations of the so-called Paleo diet, but they consist mainly of fish, grass-fed pasture raised meats, vegetables, fruit, roots, and nuts, and exclude grains, legumes, dairy products, salt, refined sugar, and processed oils) in 2003. Assuming she followed it strictly, I would rate it about 95, based on our past LRDI (mainly dietary) findings for different diseases. Then, in 2007, she started NMES. Her progress, if any, was minimal. When she switched to her present strict diet, which I would rate at 99 (I don't know whether there's a strong case for the meat as a healer based on previous LRDI findings, but if she's eating organ meats from grass-fed free-range animals, meat probably won't hurt), the NMES results increased dramatically.

If she had received the NMES when her diet was 40, there probably would have been zero gain, since the poor diet was continually destroying the myelin sheath (the electrically insulating layer around the axon of a neuron whose degradation is a characteristic of MS). Even receiving the NMES when her diet was 95 didn't do very much. It was only when her diet hit near perfection that real change occurred. So, if someone were to run tests of the efficacy of NMES on many MS patients, ***the spectrum of responses they would see would be a mirror of the quality of the diet (or, more generally, the degree of cause removal from whatever source), and tell relatively little about the efficacy of NMES.***

This means that if we see test results of a new 'treatment' performed on a number of patients who have the average American diet (the fact that they are 'patients' [with chronic or infectious disease] is one strong sign that they probably do have a poor diet), and the test results don't show much improvement, ***it may tell nothing about the quality of the treatment!*** If all the test subjects were like Dr. Wahls pre-Paleo, and they had received NMES, we probably would conclude that NMES doesn't work for MS. The more accurate conclusion might be that it doesn't

work for people with MS when the dominant cause(s) is still present; in fact, ***why would one expect it to work under those conditions***?

But, that's the reality of many medical 'treatments' today. The cause is not addressed, 'treatments' are administered, and there is a wide range of responses. The so-called 'incurable' diseases, like MS, are never 'cured' because the true cause(s) is never removed.

Evaluation and Selection of Potential Treatments in the Absence of Cause Identification and Removal

Even though we had not examined drugs or other advanced technologies for potential discovery in our 2007 LRDI MS study, I wanted to see whether we would have identified NMES (or something similar) as a potential MS treatment using LRDI without treatment constraints. So, I looked at our taxonomy of roadblocks listed in the 2007 MS study, identified some key areas necessary for healing Dr. Wahls' residual problem (gait and walking difficulties before starting the improved diet), generated a query, and inserted it into Medline. Even using a fairly strict proximity form of the query to limit retrieval volume, I retrieved thousands of records from 2007 and before. There were a number of electrical stimulation techniques that had some successes in improving motor function in the past for a wide variety of diseases and injuries, there were other techniques such as growth factor administration that had degrees of success, but all the techniques had mixed results in terms of healing effectiveness.

Then I realized the connection of the mixed results with the findings of the previous section. All the papers I was reading where they did tests/trials on human subjects were being performed on people with vastly different diets, different causes of their problem, different practitioners, different immune/neural/endocrine/circulatory system strengths, etc. That's probably why there were mixed results with all these techniques, most of these results being poor. I was probably seeing more the *spectrum of level of cause present* than I was seeing efficacy of technique. What could I really conclude from these papers? They told me nothing about what could be expected in terms of damage reversal if the test subject had a pristine diet, or had other causes fully removed, or had different practitioners, or had different immune system biomarkers. In essence, while all these papers have the appearance of high-quality research, and have passed rigorous peer-review et al, many are intrinsically worthless for decision-making. They don't tell the analyst what could be done if the correct parameters were known about each treatment.

NMES, in particular, is elicitation of muscle contraction using electric impulses. It has been used mainly to enhance athletic performance and for rehabilitation from injury, stroke, etc. In many of these applications, the cause is known, and is not being repeated. In MS, the situation is very different. The cause(s), whether diet alone or diet in conjunction with co-promoters, operates on a continuing basis to destroy myelin sheaths and produce other damage. In these non-MS applications, NMES may show effectiveness, but for the MS and similar applications, cause probably has to be removed preceding (or in parallel with) the application of NMES before significant healing can be demonstrated.

Extrapolation of the MS Results to Other Diseases

The LRDI approach circa 2007 used for the MS study (two generations behind the present LRDI approach) is not limited to MS. It is applicable to any chronic or infectious disease, and in some short studies I have done, could also be used to accelerate healing of wounds and injuries. In particular, for those diseases where diet plays a major role in determining whether or not the disease symptoms will occur, as in Dr. Wahls' case, the 2007 version of LRDI would probably be sufficient to identify diets that may have the same effect for other diseases that Dr. Wahls' diet had for MS.

I firmly believe that the present incarnation of LRDI can be applied to any chronic or infectious disease, and for those whose causes can be identified, can generate results at least as good as those of Dr. Wahls, and probably better. Unfortunately, almost all the funding for healing from these diseases is focused on 'treatments' without understanding or eliminating cause. These have been, are being, and will continue to be dead-end approaches. They involve kicking the can down the road without addressing fundamental causes.

The Main Roadblock of Biomedical Literature Deficiencies

One final caveat. The LRDI approach in its purest state is based solely on the medical literature, and any items not contained in the medical literature will not be reflected in LRDI results. To obtain these extra-literature results, experts need to be brought in and/or other information sources need to be accessed. There can be serious problems with the quality of what is placed in the literature due to poor or even fraudulent research (e.g., Stapel's fraud in psychology research [17]; fraud in retracted literature [18]; publication misconduct in oncology [19]; ethics of ghost authorship [20]), and what is omitted from the literature, either from lack of funding or blockage of publication by

those associated with the journals. The recent book Merchants of Doubt [21] describes how the literature has been skewed deliberately to protect the interests of industry and government. I have published a recent document that has expanded on this deliberate skewing [22], and shown that the tangible incentives for sponsors in industry and government and for performers in industry, government, and academia are mainly to promote findings favorable to industry and restrict findings unfavorable to industry. It is very difficult to get hard data showing actual bias mechanics, since sponsors and journal gatekeepers can argue that rejected studies or proposals are due to poor quality rather than any decision-maker bias. In [22], I used the example of a study in Microwave News [23], where publication of EMF effects in a specific journal resulted in studies mostly favorable to the industry. The editors and reviewers could always make the argument that those studies were the highest quality; how could that be refuted, except with an expensive and time-consuming independent analysis.

For the MS study, there were mixed results in the literature with a number of potential causes, food and otherwise. How many of these mixed results were due to actual medical uncertainty and how many were due to deliberate skewing of the literature? That's a strong reason why Dr. Wahls' recommended diet and the diets that could be generated from our findings focus on foods and food combinations that are hard to refute as beneficial. This to some degree is the precautionary principle approach.

DEVELOPMENT OF LRDI

Initial LBDI Study on Biowarfare Agent Defense

The remainder of the article describes the development of LRDI, and some of the insights gained in the process. My interest in LBDI started in 1999 when, as an employee of the Office of Naval Research, I sponsored a study by Swanson and Smalheiser on Biowarfare Agent Defense [24]. The purpose was to identify potential biowarfare agents based solely on the published research literature. This would help avoid surprise against foreign employment of unexpected biowarfare agents. The specific application was the first to have gone beyond the purely medical with the literature-based discovery approaches.

Journal Special Issue on LRDI Technique and Medical/ Technical Studies

After this study was published, I began to develop my own variant of the technique now called LRDI. This work culminated in Guest Editing a Special Issue of Technological Forecasting and Social Change in 2008, which included eight papers from our group [2-9]. Four of the papers were on medical topics (Raynaud's Phenomenon [RP] [4], Cataracts [5], Parkinson's Disease [PD] [6], Multiple Sclerosis [MS] [7]), and the fifth was on a technical non-medical topic (Alternative Water Desalinization Approaches) [8]. All of the studies were of the open discovery system (ODS) type, where one starts with a problem (e.g., the disease) and identifies solutions (e.g., preventatives, treatments).

The approach used in the medical LRDI papers to identify discovery was through a query that contained terms of disease characteristics to be eliminated. This query was intersected with classes of potential discovery (we limited these classes to non-drugs non-advanced technology; they were mainly foods and food extracts), and those papers in the retrieval that included the name of the disease under consideration were eliminated from further analysis for discovery (they were prior art). Typically, we had hundreds of papers in the prior art category. We had hundreds of papers in the discovery candidate category, and we selected a sub-set for validation of no prior art that we published as potential discovery. Typically, half the papers that underwent validation were prior art. Thus, our total results included many papers of prior art and many papers of potential discovery. We generated a comprehensive report [10] that included much of this data on prior art, as well as some of the potential discovery data.

In the published papers, we presented sample results from prior art, directly-related potential discovery and indirectly-related potential discovery. We did not present treatment protocols. Thus, for each disease examined, our research product was identifying hundreds of papers describing potential preventatives/treatments, probably comprising over a hundred different 'treatment' concepts. In order for these results to be implemented, they had to be culled down to perhaps the ten or twenty most important. This is a difficult procedure because of unknown synergies, positive or negative, that could arise from different combinations of these potential 'treatments'.

The numbers of potential combinations of the ten or so most important 'treatments' are staggering. As an example, assume we had 100 potential 'treatment' concepts to be considered for implementation into a treatment protocol, and we wanted ten of these concepts for the final protocol. The number of combinations of ten concepts in a pool of 100 concepts is given by the binomial coefficient: C=N!/((N-n)!*(n!)). Thus, if N=100, and n=10, C is approximately 10^20/10!, or 2*10^14. There is no way that this many combinations could be 1) tested in lab experiments or clinical trials to find the optimum or 2) even modeled on a computer because of the unknown potential synergies. The only feasible way for the culling to occur would be a panel of experts using their best judgments.

Next Generation of LRDI - SARS Study

In 2009, I published an LRDI study on SARS [11]. The main advance over the previous LRDI technique was the form of the query. I developed a functional form that basically expressed what outcome was desired (e.g., enhance humoral immunity, restrict viral entry, etc). Combined with proximity search capability, this query proved to be a more effective filter for potential discovery than previous filters. It could also be applied to full text, rather than limited to Abstracts as before.

One important finding of the SARS study came from the Background literature review. Approximately 8000 people worldwide presented with SARS symptoms, of whom about ten percent succumbed. This was not a random ten percent. The people who succumbed had significant co-morbidities and weak immune system parameters. None of the drugs worked; the effective treatments were good hygiene, isolation, and quarantine. What kept the 90% alive was a strong immune system; therefore, ***strengthening the immune system became the target for the discovery study***.

Bibliographic Coupling to Enhance Potential Discovery

In 2010, I also published an LRDI study on the relationship between Parkinson's Disease (PD) and Crohn's Disease (CD) [25]. PD is a neurodegenerative disease while CD is an autoimmune disease, and I questioned whether there could be any common features. This was the first of my LRDI studies that was the closed discovery system (CDS) type, where one starts with two problems, or a problem and a solution, and searches for mechanisms/features that link them. I combined two approaches for identifying common features in two literatures: text-based and citation-based. The text-based approach was to identify records in each literature that contained common phrases. Now, this could be done at the full-text level, at the Abstract level, at the title level, or at combinations of all three levels. For demonstration purposes, I used common phrases in titles. The citation-based approach was to identify records that had common references. For this component, I used bibliographic coupling.

What was the value of combining a text-based approach with a citation-based approach? Methods that use a text-based approach only, such as the excellent Arrowsmith software [26], tend to produce thousands or tens of thousands of these intermediate common phrases, depending on the size of the literatures linked. Since the evaluation of each phrase for potential discovery requires reading the records associated with the phrase, the problem quickly becomes infeasible without provision of additional filtering criteria. Arrowsmith has a number of built-in filtering options [27], and I have developed my own filtering approach based on phrases identified through document clustering and factor analysis. I wanted to determine whether bibliographic coupling superimposed on text phrase matching could provide an even more effective filter.

There were three major themes that unified the PD and CD literatures: Genetics; Neuroimmunology; Cell Death. Some new concepts at the sub-set level of the main themes were identified. The synergy of matching phrases and shared references provided a strong prioritization to the selection of promising matching phrases as discovery mechanisms.

Second-Generation Improvement of LRDI Technique - Vitreous Restoration Study

We are presently completing a study on vitreous restoration (vitreous is the gel between the lens and the retina in the eye; its degradation can enhance development of cataracts in the lens and more serious retinal diseases). We use an improved version of the functional query first shown in the SARS study, including proximity searching capability. We use a text-based query approach in concert with a citation-based query, which exploits the strengths of each

approach and eliminates the weaknesses. We have removed the previous restrictions on non-drug non-advanced technology discoveries only, and are considering all potential forms of treatment. We are finding that general systemic and local problem-focused treatments are both required for optimal healing, but treatment effectiveness will be strongly related to the ability to identify and remove causes of disease. We are placing more effort on identifying the widest spectrum of potential causes for vitreous degradation, in order to insure that our potential treatments cover the widest spectrum of causes possible. We are finding that a number of potential causes have not been researched in the literature, and have identified these as research gaps. Finally, as in Dr. Wahls' MS research, we also have skin-in-the-game (see Appendix) in this study.

LESSONS LEARNED FROM LRD STUDIES

Co-Promoters

For any disease, the main parameters seem to be the 'signature' of toxic stimuli (one aspect of 'cause'), the 'signature' of the state of the body (another aspect of 'cause'), the body's response to the toxic stimuli, the 'signature' of potential treatments, and the body's response to the treatments. Cell phone radiation may be toxic [16], but we know that only a fraction of users develop brain cancer. So, there must be causes in addition to cell phone radiation, or co-promoters, that result in brain cancer for those so afflicted. These co-promoters could be other toxic stimuli (e.g., toxic chemicals, poor diet, ionizing radiation, non-ionizing radiation at frequencies other than those used by cell phones, etc), genetics, or an inherently weak immune system.

Identifying Causes

In the vitreous restoration study, we are attempting to include all the above parameters in our analysis. We first attempt to identify the full spectrum of potential causes. We examine the vitreous degeneration literature to ascertain the causes identified. Then, we examine other similar tissue literatures to see whether causes for tissue degradation have been identified that were not identified in the vitreous degradation literature, and whether these causes from the other literatures are extrapolateable to the vitreous degradation problem. Finally, we consider the fundamental structure and operation of the eye, and hypothesize credible causes that have not been identified from the literatures above. Identification of the full spectrum of potential causes may be the most important step in the process, since an important principle of healing is that ***major causes need to be removed before true healing can begin***. If the cause(s) is allowed to persist, then any 'treatment' will have very limited success, at best.

Skewing of Technical Literature

Unfortunately, we have found a strong imbalance in the biomedical literature relative to 'cause'. Treatments are over-emphasized, and cause determination is under-emphasized. This may be due to lack of ideas, lack of funding, or deliberate neglect. I have addressed the latter issue in a separate article [22]. In summary, in a number of medical or medically-related areas that have commercial and/or political sensitivity, such as EMF health effects or health effects of meat products or dairy products or gluten products, there are few if any incentives for sponsors and

performers alike to relate technologies to adverse health effects, and important technical issues are either neglected in the research or possibly skewed in the reporting [e.g., 23].

Not only is there limited research on many individual causes, but even far less on co-promotional aspects. Thus, if all the potential major causes for a disease for a specific individual are not known beforehand, one cannot state in absolute terms that the spectrum of 'treatments' identified by LRDI will be effective for that individual.

Removing a Co-Promotional Cause

An example at this point may be instructive. Magda Havas published results showing EMF exposure being a potential cause of MS [28]; for people in the study who were diagnosed with MS, symptoms increased markedly when they were exposed to certain forms of EMF, and decreased markedly when the EMF sources were eliminated. Assume it is. We know there must be other factors, since not everyone exposed to EMF gets MS/MS symptoms. They could be genetic factors. However, I would assume factors like diet play a much larger role, for most people. For purposes of this discussion, assume the combination of EMF exposure and poor diet is the 'cause'. Also, let's assume either one by itself, while toxic, would not be enough to 'cause' MS. Then, if a strict diet protocol is followed, it might strengthen the neural and immune systems sufficiently that they are able to ward off the MS-symptom effects of the EMF. So, if poor diet is a strong co-promoter along with other toxic stimuli, removing poor diet as a co-promoter might be adequate to reverse symptoms. It may very well be that all 'causes' need not be eliminated for the symptoms to disappear, only the dominant ones. It would be desirable, of course, to eliminate as many 'causes as possible, but that may not absolutely necessary. The other co-promoters may still be present, but cleaning up the diet may have raised the threshold for symptoms to appear. What we don't know is whether a ***hysteresis*** effect is present for healing. In other words, ***does the diet required to reverse the disease have to be stricter than the diet necessary to prevent the disease***?

Individual Response to Toxic Stimuli and Treatments

The state of the body and its response to toxic stimuli are very important, but the former component is never even reported in most medical studies. Additionally, the state of the body and its response to treatments is very important, but the former component is never even reported in most medical studies. How can one determine the efficacy of any treatment if parameters important to the response are neglected?

As an example, one tissue regeneration therapy we examined for potential vitreous application was prolotherapy. It is a member of a larger class of connective tissue regeneration procedures that exploit the immune system to produce healing. Inflammation is induced artificially into injured or degenerative connective tissue, and when the acute inflammation heals, a stronger tissue results. This process will be strongly dependent on four major variables: cause removal; practitioner skill; immune system strength; circulatory system efficiency. Yet, almost every article, review, or meta-analysis on this general topic ***makes no mention of any of these four central variables***. And, this conclusion can be extrapolated to any healing technique that depends on the strength of the immune system for effectiveness and timeliness, which covers most healing approaches.

SUMMARY AND CONCLUSIONS

Initial Perceptions of LRDI

When we started the development of LRDI a decade ago, my world-view of medicine, medical research, and the medical literature was very different from what it is today. I (along with the other members of the research community who were pursuing variants of Swanson's LBDI approach) was using Swanson's 1986 fish-oil paper [12] as the gold standard for LBDI. I was looking for these rare esoteric needles-in-a-haystack that, when uncovered, would provide major advances toward healing from serious diseases. Before our initial Raynaud's Phenomenon LRDI study [4], I believed if we could replicate Swanson's results, that would be a major step forward, and if we could find one or two additional 'potential discoveries', that would be a breakthrough. The reality was completely opposite. We found orders of magnitude more potential discovery than any of the other LRDI researchers, as well as a vast amount of prior art. The real challenge was culling the large volume of findings into finite-sized recommendations of protocols to be followed.

From my present perspective on these initial studies, I tended to overlook the prior art in favor of the potential discovery, even though we had retrieved vast amounts of each. My reasoning was that the biomedical research and clinician communities were aware of this prior art, and if it had substantive value, they would have exploited it to the fullest extent. This was true for the other studies reported in our 2008 journal Special Issue [2-9], and for the SARS study as well [11]. Had our initial focus been on solving the total illness problem, as opposed to focusing mainly on discovery, we would have generated protocols for healing much sooner that included all prior art and potential discovery generated. Whether they would have been followed in whole or even in part without a demonstration of their healing effectiveness is another story.

Present Perspectives on LRDI

Today, I believe the focus should be on the integration of innovation (prior art) with potential discovery to identify comprehensive solutions to the total problem. I believe the present LRDI technique has the capability to provide disease reversal and damage reversal for a number of major illnesses, if not all. Its main limitations are not with the technique mechanics; these mechanics are more than adequate to provide comprehensive integrated solutions. The limitations are no longer with the culling of large volumes of findings into small recommendations; there are

probably many combinations of findings that will provide feasible healing solutions, as long as general principles and guidelines are followed.

Literature Deficiencies Major Obstacle to Progress

As we are finding with the present vitreous restoration study, and as we found with some non-LRDI EMF health effects studies, the main limitations are related to what has been published in the literature relative to what could have, and what should have, been published, and the quality and objectivity of what has been placed in the literature. Unfortunately, I have many more reservations and much mistrust about what is published in the overall biomedical literature than I had when I started LRDI development, especially on topics that have potential commercial and/or political sensitivity. Many potential causes cannot be identified with certainty because of 1) necessary research that was not done, or 2) necessary research that was done and not published, or 3) research that was published for the purpose of sowing confusion. Thus, the potential treatments identified using LRDI should be viewed as a sub-set of those necessary to address all the potential causes. For those individuals whose disease resulted from those causes identified with LRDI, the treatments have a reasonable chance of success. For those individuals whose disease resulted from causes additional to those causes identified with LRDI, the success of the treatments identified would depend on the relative co-promotional strengths of those causes identified with LRDI to those causes not identified with LRDI.

Preventatives/Systemic Treatments

We have done about a half-dozen LRDI studies in mainly different medical areas. Since most of the completed LRDI studies focused on dietary treatments, some conclusions can be drawn across studies. Most of the dietary items identified in the MS study tended to be reflected in the other studies; additionally, one section of the MS study showed the commonality of potential preventatives/ treatments among the major neurodegenerative diseases. The list of potential treatment items (reduction/ elimination of specific causes; general additions to diet/ lifestyle; specific additions to diet/ lifestyle) could apply to these other diseases as well. They appear to be foundational dietary factors for good health, almost irrespective of disease, and could be viewed as preventative/ systemic.

The preventative/ systemic treatment component tends to be anti-inflammatory anti-oxidant anti-AGEs (advanced glycation end products). It is aimed at removing the external stresses and toxic loads from the immune, neural,

endocrine and circulatory systems, thereby providing a foundation/ setting-the-stage for increasing the effectiveness of the focused treatments. The **core of the preventative/ systemic treatment results tends to be whole foods**, due to the synergies provided by the combinations of their components, and the hormetic nature of these components at physiological levels when operating in concert. **Fruits and vegetables are highly recommended across the studies**, including those rich in flavonoids, polyphenols, and anthocyanins, and especially the sulfur-rich cruciferous vegetables. **Isoflavones** (e.g., fermented soy) tend to rank high, as well as selected **herbs, spices, and probiotics**. **Omega-3 fatty acids**, in the form of wild fish (e.g., salmon, sardines), walnuts, and flax seeds are mentioned prominently, as are **algae, seaweed, and other sea vegetables**. The desirability of **caloric restriction** is seen in all the studies, as is the desirability of **minimal/low-temperature processing to reduce AGEs**. There may be slight differences across diseases.

In our present study on vitreous restoration, I examined a number of tissue regeneration literatures. One common theme in the tissue degeneration associated with disease was the presence of significant AGEs in many of the deteriorated tissues. To test how widespread this effect was, I identified 140 major diseases. I then selected twenty of the most prominent, and examined their core literatures for the presence of AGEs articles. ***Every one of these twenty major disease literatures contained one or more (some very many more) articles associating the presence of large amounts of AGEs to the disease.*** One can conclude that control of excessive AGEs in body tissues is a foundational requirement for health/healing.

AGEs are contained in different foods in different amounts, they are increased by high-temperature food processing, and they are produced endogenously by e.g. reactions of proteins with glucose and ascorbates. Thus, to decrease AGEs in tissues, low AGEs foods should be selected when other characteristics are equal, lowest temperature processing of foods (while maintaining safe conditions) should be used if possible, and sugars et al should be minimized to avoid endogenous production of AGEs.

Focused Treatments

The focused treatments target the specific characteristics of (damage done by) the disease, such as demyelination in MS (removal of the myelin sheath), dopamine reduction in PD, and vitreous degradation in the present study. For the vitreous restoration study, where restrictions on types of treatments were removed, it is clear that focused

treatments, whether from prior art or discovery, will be quite different across diseases. Thus, both systemic treatments for 1) strengthening the major systems in the body and 2) removing the causes of disease followed by, or perhaps in parallel with, 3) focused treatments to accelerate healing/symptom removal are required for maximal timely healing.

Other Applications

The above discussion has centered around medical applications, since they were the focal point of most previous LRDI studies. However, as our water purification LRDI study [8] showed, potential discovery equal to or greater than that from the medical studies may be possible for non-medical technical problems. Our latest LRDI incarnation can be easily adapted to identifying e.g. new biofuel sources, new carbon sequestration techniques, more efficient solar cell materials and structures, more sensitive environmental pollution detectors, more effective cyber-security concepts, etc.

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APPENDIX - Skin-in-the-Game

Skin-in-the-game is a concept that gained popularity in analysis of the world-wide economic collapse in Fall 2008. It reflects the level of risk participants assume in a venture. In the economic sphere, it was used in a negative sense, where organizations would trade toxic securities, knowing that they would not be adversely affected by the consequences. In traditional new aircraft or submarine development, the architects would accompany the maiden voyage, insuring they would accept the level of safety they were willing to impose on others.

In the traditional research enterprise, encompassing the full range of sponsors and performers, this is usually not the case. If there is skin-in-the-game in any sense, it is reflected in how their careers will be affected by the awarding of grants and/or the results of the research, not how they themselves will be affected by the technical or medical findings. However, most of these participants would undoubtedly be gratified by positive research outcomes.

In the recent reversal of MS reported, Dr. Wahls had skin-in-the-game. She was an MS patient, and was progressing toward an advanced stage. The research that she did, and especially the experiments she proposed, were done with the knowledge that she would try them on herself. This meant her interests went well beyond doing the type of research that would lead to future grants (although that will certainly be an outcome of her research), or beyond doing the type of research that would lead to increased publications and citations (although that will certainly be an outcome of her research), etc. Her interests were fully aimed at solving a problem, and doing whatever was necessary to achieve that end. That affected how she did the research, the level of detail she examined, and how she did the final culling from all the data available to a workable protocol.

In the end, she selected what I view as the most benign approach for reversing MS, *which is most appropriate for self-experimentation*. She selected commonly edible foods as her protocol, based on much research concerning the nutrients in these foods. To reverse the damage from MS, she eventually selected the higher technology approach of NMES, which raised the risk of her protocol. However, ***the NMES only appeared to be very effective after the strict dietary protocol was instituted***.

The vitreous restoration LRDI study also involves skin-in-the-game. There are tens of millions of people in the USA who are afflicted with vitreous degradation; I am one of them. So, in addition to my usual motivations for furthering LRDI research, I am also highly motivated to solve the vitreous restoration problem within my lifetime. I

find that I have approached this LRDI problem quite differently from those in the past. In past studies, I was content to do proof-of-principle demonstrations with a few relevant examples, with the assumption that once the technique was available, interested sponsors and full-time researchers would move the findings forward. I investigated some causes, and some solutions. In the present study, I and my collaborator are including ***all potential causes***, from the vitreous degradation literature, from related literatures that might be extrapolateable to vitreous restoration, and even those not identified but which may be possible based on fundamental biological mechanisms. I am examining thousands of Abstracts in detail, as compared to many hundreds in previous studies, to insure that no stone is left unturned. With skin-in-the-game, I am willing to do whatever is necessary to identify potential solutions. While papers et al may result, the primary goal above all else is to solve the problem. This one fact may be at least as important as all the above put together.

In aiming for this goal, we have done substantial upgrades to our queries, to our target specifications, and to how we evaluate promising treatments. The final goal is to identify the package of potential discoveries and prior art that, in synergy, will optimize the chances for vitreous restoration. In parallel, as Dr. Wahls did, I am self-experimenting with some of the more promising approaches we have identified. I cannot wait for sponsors to support lab tests and clinical trials to test out our findings, and especially the combinations. As a result, I find myself making similar testing decisions to those of Dr. Wahls. I select the most benign items for systemic treatment and focused treatment as well. This is a direct result of having skin-in-the-game. In my view, this is how research should be conducted, and having people with skin-in-the-game in the sponsor organizations would be extremely beneficial to the conduct of research and elimination of disease as well.

AUTHOR BIOGRAPHY

Ronald Neil Kostoff received a Ph. D. in Aerospace and Mechanical Sciences from Princeton University in 1967. At Bell Labs from 1966-1975, he performed technical studies in support of the NASA Office of Manned Space Flight, and economic and financial studies in support of AT&T Headquarters. He invented many concepts, including the Orbiting Molecular Shield (aka Wake Shield). This concept pioneered the capability of high vacuum in low orbit, presently exploited by all manned space vehicles. His initial aero-braking research pioneered the Aero-Assisted Orbit Transfer sub-field of Orbital Transfer Vehicles. His economic and financial studies resulted in potential savings to the Bell System of over one billion dollars.

At the U.S. Department of Energy from 1975-1983, he managed the Nuclear Applied Technology Development Division, the Fusion Systems Studies Program, and the Advanced Technology Program. He led scientific delegations to the Soviet Union on fast pulsed fusion systems and fusion-fission hybrid reactors. He led panel reviews of two major fusion concepts, Migma and Riggatron, and managed the classic reviews of the Offices of Basic Energy Sciences and Health and Environmental Research. He published numerous technical papers in the fields of pulsed fusion operation, impact fusion options, and fissile fuel production using advanced breeders.

At the Office of Naval Research from 1983-2008, he was Director of Technical Assessment for ten years. He managed the selection, resource allocation, and review of Accelerated Research Initiatives, funding-enhanced multi-disciplinary programs that constituted about 40% of ONR's budget. He invented and patented (1995) the Database Tomography process, a computer-based textual data mining approach that extracts relational information from large text databases. After managing the Navy Laboratory Independent Research Program for five years, he established a new effort in textual data mining. His interests continue to revolve around improved methods to assess the impact of science and technology, incorporating maximal use of the massive amounts of data available. In 2006, he received a full-spectrum text mining system patent. After retiring from the MITRE Corp. in 2009, he became a Research Affiliate with the School of Public Policy, GA Tech, where he continues the work in textual data mining.

He is listed in Who's Who in America, Who's Who in Science and Engineering, and 2000 Outstanding Intellectuals of the 21st Century. He testified before the Canadian Parliament in June 2002 on Peer Review for S&T. He has published over 200 papers on technical, evaluation, and text mining topics, and has edited four journal special issues since 1994 (Evaluation Review [Feb 94], Scientometrics [July 96], Journal of Technology Transfer [Fall 97]; TFSC [Feb 08]).