# The Cancer 'Brain-Mind'

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# *Abstract*

In 1979 and based on some inferred features of ‘slow’ viruses and lentiviruses, we proposed the DNA must be the repository of long-term memories in living systems (LTM)… particularly in brain and the immune system (Smith, 1979). Our analyses suggested that *a priori* changes from adenine*thymine-rich regions to guanine*cytosine-richer regions in non-proteomic regions of the genome then give rise to *a posteriori* byproducts comprising elements of LTM (e.g., immunoglobulins, unique T-cell receptors, odorant receptors, and neural networks; Smith, 1979; Smith, 2003a). Because slow viruses and lentiviruses contribute to dementia in brain, we also inferred that an analogous ’immune dementia’ could be anticipated, and would be associated with dysfunctions in the immune system (Smith, 1979; cf. Sigurdsson, 1954a; Sigurdsson. 1954b; Sigurdsson, 1954c). We subsequently reported that HIV/AIDS is one manifestation of the anticipated immune dementia (Smith, 1984).

Our investigations of HIV and AIDS, and their implications for LTM, then led to the discovery of autotoxicity, autotoxicity and context-specificity (Smith, 1983; Smith, 1984). Autotoxicity, which comprises transmissible and infectious non-nucleic-acid cellular substituents and which subsumes all prions, is known to affect brain and mind.

Autovirulence comprises transmissible and infectious virus secondary small RNA particles that often contribute to ‘hit-and-run’ and ‘beneath-the-radar’ epigenetic phenomena and syndromes. Stress-activated autovirulence (e.g., associated with Epstein-Barr virus [EBV] and some adenoviruses) is implicated in the etiologies of many genetic, epigenetic and epigenomic phenomena (Smith, 2003b; Fisher, 2009). These include: autoimmune disorders; chronic fatigue syndrome; molecular mimicry; schizophrenia; autism spectrum disorders (ASD); schizophrenia; aneuploidies and other congenital conditions; *de novo* mutations; cancers; et al.

This report focuses on neuropsychiatric consequences of autovirulence. Phenomenological observations of more than 50 cancer patients during a 4 month period at a California cancer radiation therapy clinic and, separately and independently, during a 3 month period at a Mexico cancer chemotherapy clinic, now reveal a potential cancer 'brain-mind’. The phenomenon is observed in approximately 70% of the cancer patients. Because of known effects of radiation and chemotherapy on DNA, it is not unreasonable to presume that radiation therapy and chemotherapy can affect LTM and G*C **::** A*T base-pair ratios. Yet, insofar as stress-activated EBV can contribute to distortions in one’s sensorium (e.g., in ASD and schizophrenia), our observations pose an important conundrum. To wit, do stress and anxiety that may be associated with disorders in common sense contribute to cancers (cf. Smith, 2007a; Smith, 2007b; Smith, 2008/2009)? Alternatively, is there a neuropsychiatric cancer 'brain-mind’ (perhaps associated with stress-activated autovirulence) that may be unrelated to disorders in common sense?

In this presentation, I report both possibilities … along with elements of the potential cancer 'brain-mind’. Importantly, these findings underscore the need for the detection, assessment and management of stress in medical and clinical professions. Our findings

also reveal a need to disambiguate among the effects of radiation therapy, chemotherapy and autovirulence on brain and its sensorium. Finally, our findings affirm the theoretical and experimental potential of our recently patented preliophic moleculator invention (Smith and Shadel, 2010).

**Key Words:** Cancer; Brain-Mind; Logistic Reasoning; Logistic Intelligence; Error Analysis; Fault Analysis; Autovirulent Factors; Autism; Schizophrenia; Autotoxicity; Autotoxins; Autovirulence; Autovirions; Context-Specificity; Infectiousness; Transmissibility; Epstein-Barr Virus; EBV; Adenovirus; Hyper-endemic; *De Novo* Mutations; Autoimmune; Evolution; Etiology; Pathogenicity; Causality; Science; Philosophy of Science; Parsimony; Ockham's Razor

**Acknowledgments**: My mother Artisse Macomson Smith (who passed away on this day in 1998); Fadia Jamal-Eddine; Filiberto Muñoz MD; Carlos Manzilla MD; Adrian Robinson MD; Luis Cedeño Paz MD; Ann Bromley; Earl K. Maxie MD; Todd R. Smith; Nicole M. Smith PhD; Nadia Jamal-Eddine; Staff and cancer patients at the Valley Cancer Institute (Culver City, CA) and the San Diego Clinic (Tijuana, Baja California Mexico); various financial Angels; various professional Angels; Brigitta “Anu” Wissmann; George Gaboury and the San Francisco Tesla Society; Paola Barbieri PhD; Susan Collins; Anthony Fulker; Nidia Cota RN; Can Altinbay; and numerous others.

# *The Cancer 'Brain-Mind': How did we get here?*

*Some Advanced Organizers*

- 1979 theory that DNA must be the repositories of Long-Term Memories
- 1979 projection that there could be 'immune dementia' if brain and the immune systems are parsimonious
- 1981ff findings of acid-labile alpha-interferon in most laboratory studies of persons with HIV/AIDS
- 1975 recognition of a need for helping unknowingly needy ,,, and worried well
- Friends can be good medicine
- Common sense and disorders in common sense
- Stress-activated viruses
- Preliophics – New Ways of Thinking and Novel Approaches to Science
- A cancer 'brain-mind'
- Encapsulation of findings
- Recommendations
- Bibliography and references

# *1979 theory that DNA must be the repositories of Long-Term Memories*

## Abstract for a 1979 Presentation in Which the Notions of DNA is the Repository of Long-Term Memories and “Immune Dementia” Were Proposed

*Abstracts*, 7th MEETING OF THE INTERNATIONAL SOCIETY
FOR NEUROCHEMISTRY, Jerusalem, ISRAEL - September 2-6, 1979, p. 590.

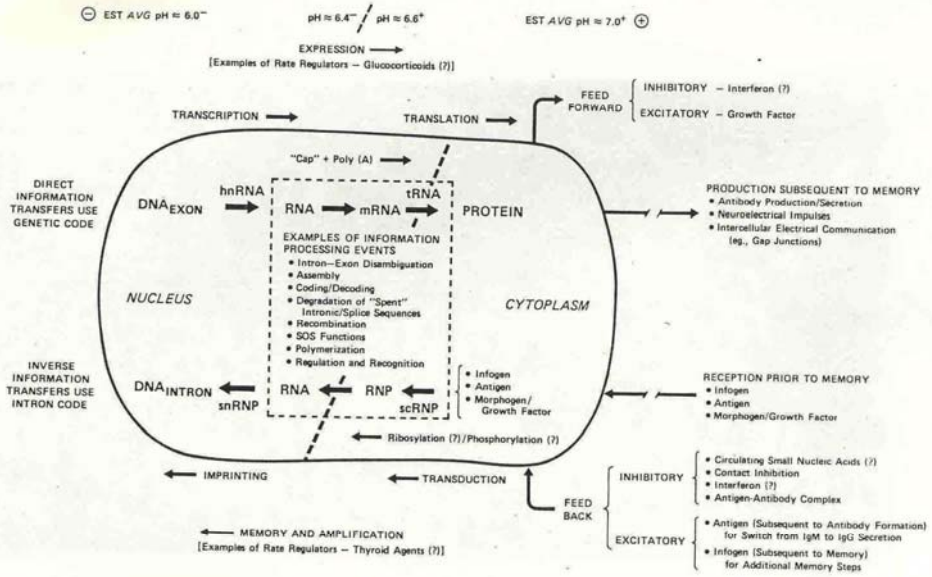
"LONG-TERM MEMORIES: Where Does The 'Buck' Stop? – Toward a Testable Theory of Debugging the Molecular Basis of Long Term Memories in Living Organisms"

Roulette Wm. SMITH, PhD
School of Medicine, University of California, San Francisco
Editor – INSTRUCTIONAL SCIENCE & HEALTH POLICY AND EDUCATION

A review of the literature on the molecular basis of memory reveals no evidence supporting extant views that RNA and/or proteins may be the repository of long-term memories (LTM) in living organisms. This study reveals a plausible and testable model based on DNA modifications, insertions, transpositions and reverse transcriptions which is more consistent with published reports. The theory may explain the "slowness" of slowly transmissible infectious agents, certain cancers, and a variety of other clinical entities. Independently of the accuracy of the theory of LTM, we show that no model of LTM can be complete without the definitive evaluation of DNA as the ultimate repository of information. This thesis enables one to discuss the evolutionary and developmental basis of memory, and to describe experimental technologies considered essential for the explication of memory. The study also reveals the potential for studying memory at the cellular level with differentiation being analogous to LTM and autophagy/cellular optimization being more analogous to STM. Implications for a variety of multidisciplinary issues are described, including aging, evolution, DNA dynamics, virology, experimental design, theory formulation and the philosophy of science, and, the search for the elusive engram in psychology.

TABLE 5

# SCHEMATIC REPRESENTATION OF NORMAL INFORMATION TRANSFERS IN SELECTED EUKARYOTIC CELLS

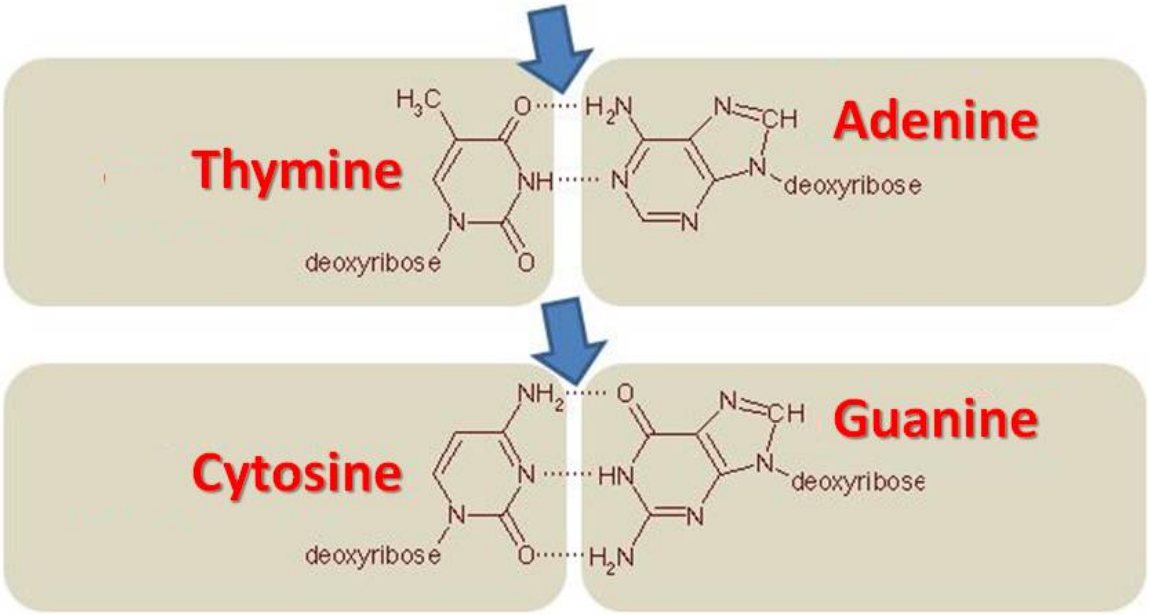


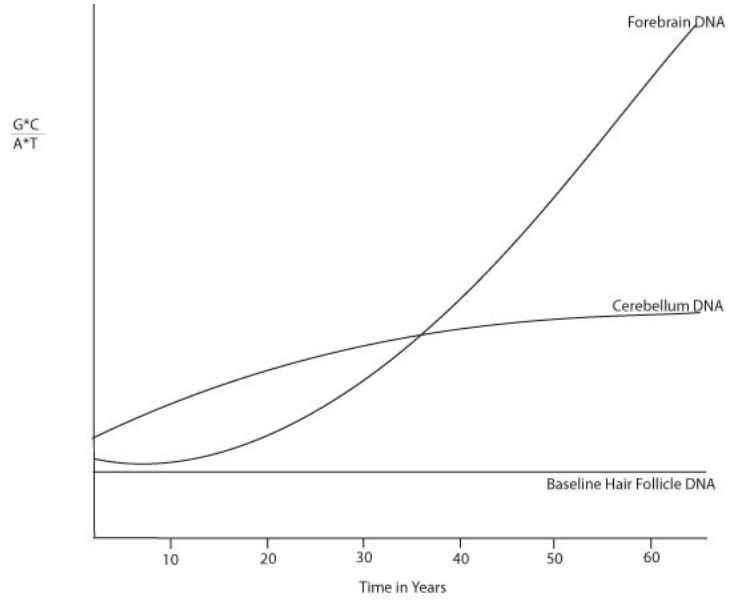

DNA – Major Storage/Memory Molecule
RNA – Major Information Processing Molecule (Along with Nucleoproteins)
PROTEIN – Major Structural/Functional Molecule

INFOGEN – Produces Memory Without Replication
ANTIGEN – Produces Memory Separate from Replication
MORPHOGEN – Produces Memory with Replication (Differentiation)

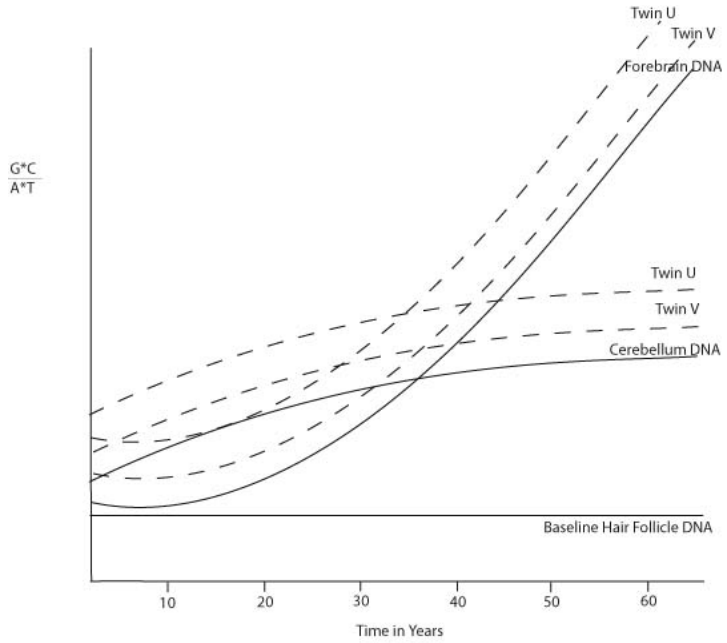
Notes:
- Transmissible infectious agents can emulate or subvert any type (direct/inverse) information processing event or structure.
- Viral early events often are analogus to inverse information processes, while viral late events may mimic direct or inverse information processes.

Genetic diseases can cause aberrations in most structures and processes.
Tumor initiators and promotors may have separate actions along the inverse information pathway.
Radiation may preferentially damage intronic sites.
Molecular information proceeds, in part, along 3-dimentional micro-pH gradients.

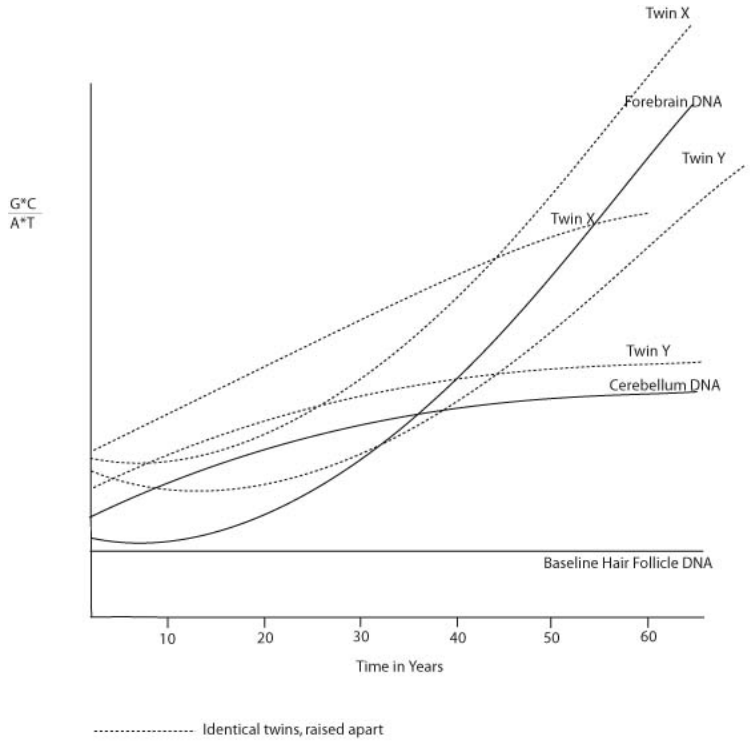

Thymine
Adenine
deoxyribose
deoxyribose
Cytosine
Guanine
deoxyribose
deoxyribose




Typical GC:AT ratios for an average human being




— — — - Identical twins, raised together




---------- Identical twins, raised apart

*1979 projection that there could be 'immune dementia' if brain and the immune systems are parsimonious*

| **Brain** | **Immune System** |
| --- | --- |
| Changes from A*T to G*C | Changes from A*T to G*C |
| No cell replication / division | Cell replication / division |
| → axon formation | → immunoglobulin formation |
| → dendrite formation | → T-cell receptor formation |

# *Acid-labile alpha-interferon is found most autoimmune disorders and in persons with HIV/AIDS*

- Exposure of Increasing titers of Epstein-Barr virus in cultured cells gives rise to increasing titers of alpha interferon (Kikuta et al., 1984)
- Exposure of Increasing titers of Epstein-Barr virus in cultured cells gives rise to acid-labile alpha interferon (Kikuta et al., unpublished / 1984)
- EBER-1 and EBER-2 are small RNAs associated with Epstein-Barr virus
- VA-I and VA-II are small RNAs associated with some adenoviruses

***Could EBER-1 and/or EBER-2 (or VA-I and/or VA-II) function as aberrant transfer-RNAs, thereby giving rise to epigenetic and/or epigenomic byproducts?***
The preliophic moleculator was designed to explore this and other questions (e.g., are increasing end-point titers associated with the scrapie agent / prions a function of replication, biological fission or some other molecular mechanism).

## *1975 recognition of a need for helping unknowingly needy ,,, and worried well*

The notion of 'unknowing neediness' and 'worried wellness' also can be derived from a 'commonsense' application of a paradigm and model for social design and social engineering (Smith, 2006; Smith, 2007; Smith, 2008; Smith, 2009). To pursue the challenge of identifying and assisting unknowingly needy and worried well, we draw upon a well-know adage that:

> "Mankind may be divided into four classes:
> (1) Those who *KNOW* and know that they *KNOW* – of them seek knowledge;
> (2) Those who *KNOW* but do not know that they *KNOW* – awaken them;
> (3) Those that do not *KNOW* and know that they do not *KNOW* – instruct them;
> (4) Those who do not *KNOW* but think that they *KNOW* – they are fools, dismiss them."
>
> Salomon Ibn Gabirol (also known as Avicebron)
> In *Mibhar Hu-Peninim* [*Choice of Pearls*]
> No. 60 (circa 1050 AD)

An analysis of this adage reveals that those with and without knowledge may be partitioned, albeit somewhat simplistically, according to their education, alertness, motivation and ability to educate. The range of possibilities is even more instructive if the words "*NEED*" and/or "*HELP*" are substituted for the capitalized and italicized word "*KNOW*."

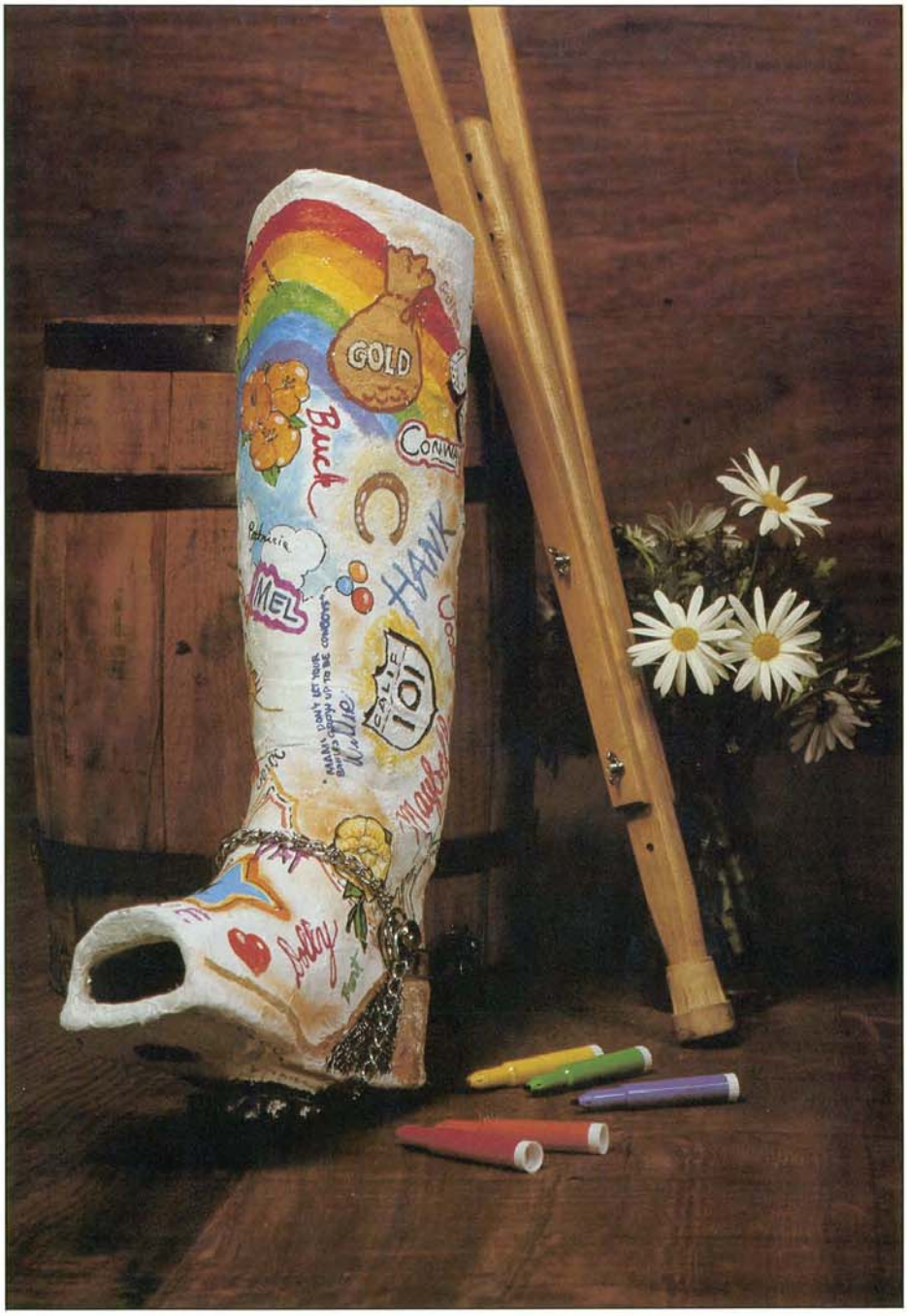
# *Friends can be good medicine*

- Good, Special or Best Friends??? (cf. Rubin, 1984)
- American Geisha Society
- Society of 'Friends'
- Friends as Angels
- 'Caring is the only daring …', Kenneth Patchen
- Is it possible to create a professional society of "best friends" in order to facilitate caring being the only daring?


***Friends can be good medicine.***

# *Friends can be good medicine.*

CALIFORNIA DEPARTMENT OF MENTAL HEALTH




# *Friends can be good medicine.*

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# *Common sense and disorders in common sense*

Although the term ‘common sense’ or its equivalent appears in virtually all languages and throughout all ages (Smith, 1988; Smith, 2006; Smith, 2007; Smith, 2008; Smith, 2009; cf. Blankenburg, 1969; Sternberg et al., 1995; Blankenburg and Mishara, 2001), there is scant literature on common sense and its disorders in any medical subspecialty, the social or behavioral science, or in literature on spirituality and the transpersonal. Even more astonishing, all persons and all languages have terms and expressions for persons with disorders in common sense (see Tables 1 and 2 in Smith, 2007; Smith, 2008) even though there are no proscriptive or prescriptive measures to deal with those disorders. Somewhat remarkably, the few exceptions in the literature generally focus on common sense vis-à-vis schizophrenia (Forrest, 1976; Bovet and Parnas, 1993; McEvoy et al., 1996; Møller and Husby , 2000; Stanghellini, 2000; Stanghellini, 2001; Sass and Parnas, 2003; Stanghellini, 2004; Lobban and Barrowclough, 2005; Uhlhaas and Mishara, 2007; Stanghellini and Ballerini, 2007; Lysaker and Lysaker, 2010; Taylor, 2010). This focus on schizophrenia, while conceptually limited, does have important molecular implications in view of a putative role of autovirulence in the etiology of schizophrenia. The obvious question is whether there may be a molecular basis underlying some disorders in common sense, and, if so, which disorders have molecular underpinnings in contrast to those disorders that may have cultural and educational underpinnings

What is common sense? Blankenburg (1969; 2001) defines common sense in terms of: (1) the relationship between cognition and action or practice, (2) the relationship between mediacy and immediacy, (3) the questionableness of the obviousness of what seems obvious, and (4) the intersubjective constitution of the world. For our purposes, *common sense* is defined as *core nurturance within a group, herd, culture, and/or organization or institution* (Smith, 2007). In regard to nurturance, most, if not all, decision-making processes within the context of the group, herd, culture and/or organization must be *appropriate* (i.e., well-circumscribed), and *no* decision-making processes within the context of that group, herd, culture and/or organization should be blatantly or flagrantly *inappropriate* (i.e., represent aberrant thinking and/or outlying behavior). Emphasis on appropriateness and inappropriateness in actual decision-making is deemed to be essential in thinking and “sense-making.” The notions of appropriateness and inappropriateness also are central to the commonality in real and expected behaviors. *Importantly, the term common sense applies to the group, collectively, and its members*

Interestingly, there is compelling evidence that ‘transmissible negativism’ (Smith, 1988), trauma and war (Smith, 2005; Smith, 2007; Smith, 2008) can give rise to divergences and disorders in common sense. This poses the intriguing challenge of finding ways to hold common sense fixed as a means of averting wars and supporting peace. At the very least, these findings present challenges to game theorists (in regards to roles of competition in peace studies; Smith 2010a) and military sciences (in regards to the roles of post-traumatic stress disorders, and post-battleground and after-war experiences) in common sense for returning veterans and for society.

In adults, disorders in common sense often present as general anxiety disorders (Smith, 2007; Smith, 2008; Smith, 2009), even though, as mentioned above, there is scant literature on common sense or in any diagnostic and statistical [DSM] reference series. In children, disorders in common sense often present as intellectual deficits in mathematics and reading skills and abilities, along with accompanying behavioral disorders (Smith, 1988).

Persons with disorders in common sense often have a profound capacity for *misunderstanding* (Smith, 2007; Smith, 2008; Smith, 2009), with there being scant literature on misunderstanding. Thus, it should not escape one's attention that helping the unknowingly needy and worried well are among the most difficult challenges pertaining to persons with disorders in common sense, and especially among returning war veterans and especially involving compliance issues in patients.

Last but not least, the evolution of common sense and disorders in common sense reveals important challenges vis-à-vis globalization and the information age. Globalization and the information age are contributing to intersecting cultural values and special interest perspectives. Political, religious, environmental and economic special interests are contributing to unanticipated and unforeseeable stress-points that now must be explicated in the interest of harmony and world order.

The focus of my research includes questions of what is common sense, what are disorders in common sense, and questions of their evolutionary, transmissible, clinical, pedagogical, biological, economic, ethical, moral and spiritual components. A principal goal is to elucidate and explicate the following issues:

- *The Evolution of Cooperation and Common Sense*
- *Teaching Common Sense in the Home, Community, Educational System, Clinics, and Transpersonal and Spiritual Institutions*
- *A Role for Common Sense in the Professions*
- *War and Post-Traumatic Stress Contribute to Divergences in Common Sense*
- *Common Sense and Peace*
- *The Economics of Common Sense and Disorders in Common Sense*
- *Common Sense in Government, Business and World Trade*
- *Stress and Common Sense*
- *The Epidemiology of Disorders in Common Sense*
- *Stress-Induced Disabilities and Workmen's Compensation Issues*
- *Autovirulent Markers in Aberrant Common Sense*
- *Disambiguating Cancers Contributing to Disorders in Common Sense and Cancers Secondary to (i.e., Derived From) Disorders in Common Sense*
- *Common Sense, Spirituality and the Transpersonal*

**Psychological and Physical Symptoms in the Propositi in 2007 Study**

| Propositi / Psychological | "A" | "B" | "C" | "D" | "E" | "F" | "X" | "Y" | "Z" |
|---|---|---|---|---|---|---|---|---|---|
| *Gender* | F | F | F | F | M | F | M | F | F |
| *Aberrant common sense* | xxx | | xxxx | xxxxx | xx | x | x | xx | x |
| *Impaired reasoning, anticipatory & problem-solving skills* | xxx | | xx | xxxx | xxx | x | | xx | x |
| *Negativism* | xxx | | xx | xxx## | | | x | x | unk |
| *Selfish* | xxx | | xxxx | xxxx | unk | X | x+ | unk | unk |
| *Witty & humorous "zingers"* | xx | | xx | x | | xx | unk | unk | unk |
| *Unconditional love for offspring* | xxx | N/A | N/A | xxx | N/A | x | unk | unk | unk |
| *Poor parenting skills* | xxxxx | N/A | N/A | xxxxx## | N/A | | xxx | unk | unk |
| *Blames others* | xxx | | xx | xx## | unk | x | x | x | unk |
| *Mood swings* | xxxx | | xx | xxx# | x | | unk | unk | unk |
| *Obsessive-Compulsive* | | xx | | ##### | # | | unk | X | unk |
| *Passive-aggressive, tardy & procrastinates* | xxx | | xxxxxx | xxxxx## | ? | | xxxx | unk | unk |
| *Internecine behavior* | x | | xxx | # | | | unk | unk | unk |
| *Suicidal ideation* | x | | unk | xxx | unk | | unk | unk | unk |
| *'My way or the highway'* | xxxx | | xxx | xxxx## | unk | x | x | xx | x |
| *Exhibitionist* | x | | x | | | | unk | unk | unk |
| *High risk sexual behavior* | xx | x | x | x | | x | x | unk | unk |
| *Constantly seeking love* | xx | ? | xxxx | xxxx# | N/A | x | x | | |
| *Interracial, interfaith, interethnic relationships* | xxx | | x | xxxx | N/A | x | xxx | unk | unk |
| *High failure rate in relationships* | xxx | x | xxxx | xxxxxx | ? | x | x | unk | unk |
| *Addiction* | x | | | | N/A | | xx | unk | unk |
| *Teetotaler* | | | x | x | N/A | | | unk | unk |
| *Aberrant distillation skills* | xxx | | xx | xxxx## | ? | | x | x | x |
| • *Impractical concerns and/or poor knowledge* | xxx | | xx | xxxx## | | | x+ | x | x |
| • *Insensitivities* | xx | | x | xxx## | | | xx | x | x |
| • *Poor introspection* | xxx | | xxx | xxx## | xxx | xx | xxx | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| • ***Poor discernment*** | **xxx** | | | **xxx##** | | | **unk** | **unk** | **unk** |
| • ***Poor mindfulness*** | **xxx** | | **x** | **xxx#** | | | **x** | **x** | **x** |
| ***Breaks agreements*** | **xx** | | **xxx** | **xxx** | | **x** | **xx** | **unk** | **unk** |
| ***Prone to mistakes, breakages & errors*** | **xxx** | | **x** | **xx##** | | **x** | **unk** | **unk** | **unk** |
| ***Misunderstandings*** | **xxx** | | **x** | **xxx##** | | **x** | **unk** | **unk** | **unk** |
| ***Does not accept responsibility*** | **xxx** | | **xxx** | **xxxxx** | | | **unk** | **unk** | **unk** |
| ***Difficulties in understanding*** | **xxxxx** | | | **xxxxx##** | | | **unk** | **unk** | **unk** |
| ***Chaos & unbelievably thoughtless (Footnote*** *Error! Bookmark not defined.****)*** | **xxxx** | | **x** | **xxx##** | | | **xx** | **unk** | **unk** |
| ***Confuses reasons & excuses*** | **xxx** | | **x** | **xx##** | | | **x** | **unk** | **unk** |
| ***Inappropriate body language*** | **xx** | | **x** | | | | **unk** | **unk** | **unk** |
| ***Narcissistic and single-minded*** | **x** | | **xx** | **xx** | | | **x** | **unk** | **unk** |
| ***Savant-like behavior*** | | | **x** | | **x###** | | **unk** | **unk** | **unk** |
| ***Irrational actions, fears, worries & risks*** | **xxxx** | | **xx** | **xxxxx###** | | | **unk** | **unk** | **unk** |
| **Interest in occult and mystical** | **xx** | | | **xxxx** | | **x** | **unk** | **unk** | **x** |
| **Physical and Somatic** | | | | | | | | | |
| ***Anxiety > 6 months & generalized anxieties*** | **xxxx** | | **xx** | **xxxxxx###** | **x** | | **unk** | **unk** | **unk** |
| ***Medicated for anxiety*** | **Yes** | | | **No** | | | **unk** | **unk** | **unk** |
| ***Rapid heat beat*** | **xx** | | | **xxx** | | | **x** | **unk** | **unk** |
| ***Sweating*** | **x** | | | **xx** | | | **unk** | **unk** | **unk** |
| ***Difficulty breathing*** | **x** | | | **xxx** | | | **unk** | **unk** | **unk** |
| ***Feeling tense*** | **xx** | | **x** | **xx** | | | **unk** | **unk** | **unk** |
| ***Muscle tension*** | **xxx** | | **xx** | **xxx** | | | **unk** | **unk** | **unk** |
| ***Neck and back pains*** | **xxx** | | **X** | **xxx** | | | **unk** | **unk** | **unk** |
| ***Headaches*** | **xxx** | | **X** | **xxx** | | | **unk** | **unk** | **unk** |
| ***Trembling*** | **x** | | | **xx** | | | **unk** | **unk** | **unk** |
| ***Irritability*** | **xx** | | **x** | **x** | | | **x** | **unk** | **unk** |
| ***Fatigue*** | **x** | | **x** | **xx** | | | **unk** | **unk** | **unk** |
| ***Easily "stressed out"*** | **xxx** | | **xx** | **xxx##** | **unk** | | **unk** | **unk** | **unk** |
| ***Stress-induced (EBV-related)*** | **x** | | **?** | **xx** | | | **unk** | **unk** | **unk** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***epigenetic disorders*** | | | | | | | | | |
| ***Psychosomatic disorders*** | **xxx** | | **x** | **xxxx#** | | | **unk** | **unk** | **unk** |

- **x** = one unit in the investigator's subjective measure of profoundness. These units are open-ended and do not represent closed Likert scales. Some subjective measures represent actual events.
- **#** = one unit in the investigator's subjective measure of profoundness during an overnight (*in situ*) visit as a house guest on December 15, 2007. These units are open-ended and do not represent closed Likert scales. Some subjective measures represent actual events.
- **unk** = unknown to the investigator because these propositi did not reside in the household, could not be observed directly or indirectly, and/or second-hand information was deemed unreliable or lacking validity.
- Gender = **F** – female; **M** – male.
- **N/A** – Not applicable.
- **? –** Insufficient information to reach a conclusion.

Bulleted points associated with "**Aberrant distillation skills"** represent negatives.

## *Stress-activated viruses*

- Epstein-Barr virus
- Selected adenoviruses
- Other stress-activated viruses
- Autotoxicity, autovirulence and context-specificity

**Diseases, Symptoms, Conditions and Syndromes Associated with EBV (Based, in part, on a 2008 PubMed search of 21141 citations)**

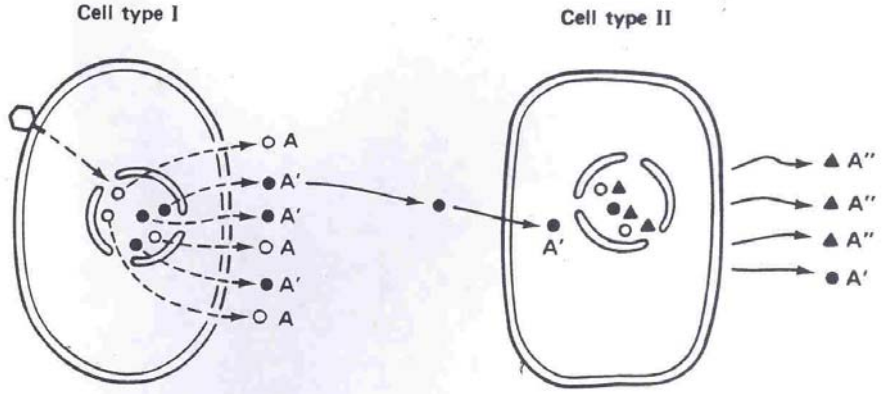
1. Aberrations in membrane and nuclear proteins
2. Aberrations in teleomeric protein complexes (Wistar study – Molecular Cell, March 29, 2002)
3. Acid-labile α-interferon (Kikuta, Mizuno and Osato 1984 study)
4. Acute cerebellar ataxia
5. Amyotrophic Lateral Sclerosis (i.e., Lou Gehrig disease)
6. Antiphospholipid Antibody Syndrome – Cervera, R. and Asherson. R. A. Antiphospholipid syndrome associated with infection: clinical and microbiological characteristics, Immunobiology 2005; 210:735-741.
7. Antiphospholipid Antibody Syndrome and Pregnancy
8. Aplastic Anemia
9. Autism spectrum disorders
10. Autoimmune Hepatitis
11. Autonomic neuropathy
12. Babesiosis; Mycoplasma Infections (also see Rasmussen's encephalitis/disease); Hepatitis A; Coxsackieviruses; Herpes Zoster; HIV-1 Associated CNS Complications (Overview); HIV-1 Associated Opportunistic Neoplasms: CNS Lymphoma; Cytomegalovirus
13. Bell's palsy
14. Bone Marrow Transplantation, Long-Term Effects (Two cases of chronic active Epstein-Barr virus infection in which EBV-specific cytotoxic T lymphocyte was induced after allogeneic bone marrow transplantation. Pediatr Transplant. 2008 Feb 6)
15. Brachial plexus neuropathy; Brachial Neuritis; Neonatal Brachial Plexus Palsies
16. Breast Carcinoma [Detection of Epstein-Barr virus in breast carcinoma in Egyptian women, Clin Biochem. 2008 May; 41(7-8):486-92; Detection of Epstein-Barr virus in breast cancers with lymphoid stroma, Ann Biol Clin (Paris). 2008 Jan-Feb; 66(1):59-62]
17. Burkitt's Lymphoma
18. Cancer "Brain-Mind'
19. Castleman's disease (HHV8)
20. Childhood Cancer, Epidemiology
21. Chorioretinitis
22. Chronic Fatigue Syndrome; Chronic Fatigue Syndrome
23. Chronic Obstructive Pulmonary Disease (COPD) - High levels of Epstein-Barr virus in COPD. Eur Respir J. 2008 Jun; 31(6):1221-6
24. Cold Agglutinin Disease; Cold Agglutinin Disease
25. Cold-induced urticaria [Ann Allergy 1983 Apr; 50(4):271-274]
26. Coma
27. Common Variable Immunodeficiency
28. Complement Receptor Deficiency
29. Crohn's and other irritable and inflammatory bowel disorders
30. Cryoglobulinemia
31. Cutaneous Manifestations of HIV Disease

32. Down syndrome, mosaic Down syndrome and other aneuploidies (e.g., Klinefelter syndrome)
33. Ear, Inner and External Ear, Inflammatory Diseases –
34. Early Symptomatic HIV Infection
35. Encephalitis
36. Epiglottitis
37. Erythema Annulare Centrifugum
38. Esophageal Lymphoma
39. Esophagitis
40. Fever of Unknown Origin
41. Fibromyalgia
42. Gastric carcinoma [Cancer Res. 2008 Mar 1;68(5):1427-35; Epstein-Barr virus associated gastric carcinoma: epidemiological and clinicopathological features, Cancer Sci. 2008 Feb;99(2):195-201; A case of Epstein-Barr virus (EBV) associated remnant gastric carcinoma arising 7 years after distal gastrectomy for EBV associated gastric carcinoma, Nippon Shokakibyo Gakkai Zasshi. 2007 Dec; 104(12):1728-32]
43. GI dysfunction secondary to selective cholinergeic dysautonomia
44. Glandular fever
45. Gianotti-Crosti Syndrome (Papular Acrodermatitis of Childhood)
46. Granuloma Annulare
47. Guillain-Barre Syndrome
48. Hairy Leukoplakia
49. Hashimoto's thyroiditis
50. Head and Neck Cancer: Squamous Cell Carcinoma
51. Hearing loss
52. Heart Transplantation; Heart Transplantation; Heart-Lung Transplantation
53. Hemophagocytic syndromes
54. Hodgkin Disease; Hodgkin Disease; Hodgkin Disease, Thoracic
55. Human Herpesvirus Type 6
56. Hypoglossal nerve palsy
57. Infantile Polyarteritis Nodosa
58. Interstitial Lung Disease in Children
59. Intestinal and Multivisceral Transplantation
60. Kaposi Sarcoma
61. Leukemias
62. Liver Transplantation; History of Pediatric Liver Transplantation
63. Lung Transplantation; Lung Transplantation; Heart-Lung Transplantation
64. Lupus Erythematosus, Acute
65. Lymphoma, Diffuse Large Cell; Lymphoma, Malignant Small Noncleaved; Lymphoma, Mantle Cell
66. Lyomyosarcoma (###)
67. Lymphoma, Non-Hodgkin
68. Lymphomatoid Granulomatosis
69. Lymphoproliferative Disorders; Lymphadenopathy
70. Lymphoproliferative Syndrome, X-linked

71. Malignant Tumors of the Nasal Cavity
72. Meningoencephalopathy
73. Mesenteric Lymphadenitis
74. Metamorphopsia (Alice in Wonderland Syndrome – Metamorphopsia is a visual illusion that distorts the size, shape, or inclination of objects)
75. Mitochondria-related – Epstein-Barr virus immediate-early protein Zta co-opts mitochondrial single-stranded DNA binding protein to promote viral and inhibit mitochondrial DNA replication (J Virol. 2008 May; 82(9):4647-55)
76. Mixed Connective Tissue Disease
77. Moebius Syndrome (Epstein-Barr virus versus use of Misoprostol or Thalidomide during pregnancy)
78. Mononucleosis and Epstein-Barr Virus Infection; Mononucleosis; Infectious Mononucleosis, Infectious mononucleosis due to Epstein-Barr virus with suspected reactivation of human herpesvirus 6 (Kansenshogaku Zasshi. 2008 Jan; 82(1):47-50)
79. Mucocele and Ranula
80. Multiple cranial nerve palsies
81. Multiple Sclerosis; Multiple Sclerosis; Integrating risk factors: HLA-DRB1*1501 and Epstein-Barr virus in multiple sclerosis, Neurology 2008 Mar 25; 70(13 Pt 2):1113-8; Epstein-Barr virus genotypes in multiple sclerosis, Acta Neurol Scand. 2008 Feb; 117(2):141-4]
82. Myelodysplasia
83. Myelodysplastic Syndrome
84. Myogenic Tumors – Posttransplant Epstein-Barr virus-associated myogenic tumors: case report and review of the literature, Am J Transplant. 2008 Jan; 8(1):253-8
85. Myopericytoma – Multifocal Epstein Barr virus (EBV)-associated myopericytoma in a patient with AIDS, Neuropathol Appl Neurobiol. 2008 Feb; 34(1):115-7
86. Nasopharyngeal Cancer [Expression of Epstein-Barr-virus-encoded small nuclear RNA in nasopharyngeal carcinomas of Aegean Turkish patients, Virchows Arch. 2008 Apr; 452(4):411-4]
87. Neuroendocrine Carcinoma – Small-Cell Neuroendocrine Carcinoma of the Nasopharynx: Report of a Rare Case Lacking Association With Epstein-Barr Virus, *International Journal of Surgical Pathology* 2008 May 28
88. Nonrhabdomyosarcoma Soft Tissue Sarcomas
89. Oculoglandular syndrome associated with reactivated Epstein-Barr-virus infection, British Journal of Ophthalmology 2008; 92(6):740.
90. Normal-tension glaucoma - Anti-Ro/SS-A positivity and heat shock protein antibodies in patients with normal-pressure glaucoma, American journal of ophthalmology 1998; 125(2):145-157; Antiphosphatidylserine antibodies are elevated in normal tension glaucoma, Clinical and Experimental Immunology. 2001; 125(2):211–215.
91. Oral Manifestations of Systemic Diseases; Some Crohn's Disease
92. Periodontitis (Patient with severe periodontitis and subgingival Epstein-Barr virus treated with antiviral therapy, J Clin Virol. 2008 Jun; 42(2):176-8)
93. Periorbital Infections

94. Pharyngitis
95. Pharyngitis, Viral; Pharyngitis
96. Pityriasis Lichenoides
97. Pneumonia, Viral; Lymphocytic Interstitial Pneumonia
98. Polymyositis
99. Posttransplant Lymphoproliferative Disease
100. Pregnancy- and Fetus-related disorders – Fetal exposure to herpesviruses may be associated with pregnancy-induced hypertensive disorders and preterm birth in a Caucasian population, BJOG. 2008 Mar; 115(4):492-500
101. Rasmussen's encephalitis
102. Reye's syndrome
103. Raynaud's disease
104. Schizophrenia
105. Severe Combined Immunodeficiency
106. Sjögren Syndrome; Sjögren Syndrome; Sjögren Syndrome; Sjögren Syndrome
107. Some sarcoidoses
108. Splenomegaly
109. Stress associated with events of September 11, 2001 is linked to loss in male babies (see <http://www.ivanhoe.com/channels/p_channelstory.cfm?&storyid=24324>)
110. Systemic Sclerosis (SSc) aka Scleroderma and CREST syndrome (i.e., **C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysfunction, **S**clerodactyly, and **T**elangiectasias)
111. Telogen Effluvium (stress- or trauma-induced premature hair-graying)
112. T-Cell Disorders; Some B-cell lymphomas and other disorders; Non-functional antibodies
113. Tonsillitis and Peritonsillar Abscess
114. Transplants, Renal
115. Transverse myelitis
116. Unilateral laterothoracic exanthem with coincident evidence of Epstein-Barr virus reactivation: exploration of a possible link., Dermatol Online Journal 2008 Jan 15; 14(1):24
117. Unusual neurologic findings in childhood (Journal of Child Neurology 2000; 15:791-796)
118. Upper Respiratory Infection
119. Viral Infections of the Mouth
120. Viral Meningitis; Meningitis; Meningitis, Aseptic
121. Vulvar Ulcerations – Picture of the month quiz case. Vulvar ulcerations resulting from acute Epstein-Barr virus infection, Arch Pediatr Adolesc Med. 2008 Jan;162(1):86-87

# AUTOTOXICITY




release of A by lytic, genetic or other non-physiological event

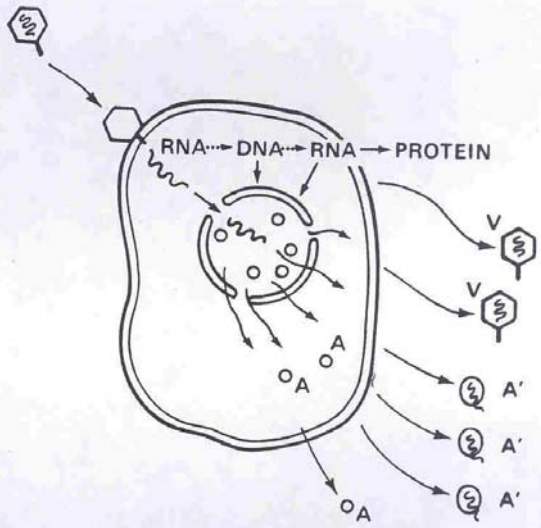
uptake and toxicity of A' causing the release of multiple copies of A'' (and sometimes A or A')

A,A' = autotoxins

Implications

1. Autotoxins are context-specific molecules which generally are ribonucleoproteins.
2. Autotoxins may be autoantigens in some autoimmune diseases.
3. Autotoxicity may mimic viral replication because of the release of multiple copies of autotoxins.
4. Experimental inoculations of autotoxins may provide false indications of natural transmissibility.
5. The Henle-Koch postulates need to take into account additional controls for autotoxins and autovirions.

## AUTOVIRULENCE

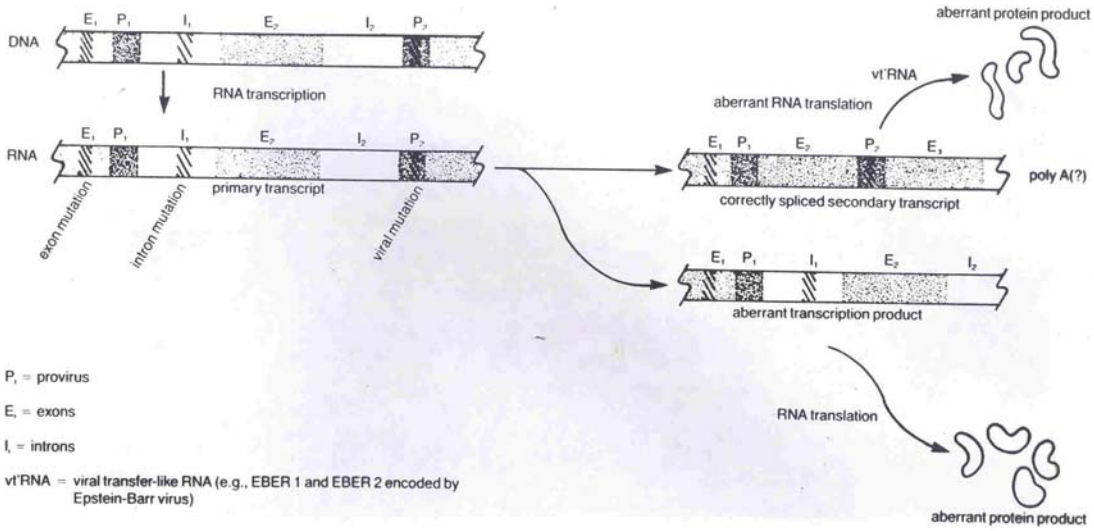



V = virus
A = autotoxin
A′ = autovirion

Implications

1. Context-specificity of autovirions generally is based on the source of the small, regulatory RNA contained within them.
2. Autovirions may be associated with some autoimmune diseases.
3. Autovirions may appear to be replicated, although the number of autovirions may depend on the transcription of some viral or other nucleic acid product.
4. Autovirions may mimic viruses both in their transmissibility and their apparent replicability.
5. "Slow viruses" may be autovirions or autotoxins.
6. Adenoviruses and Epstein-Barr viruses can produce autovirions.

## SOME EXAMPLES OF DIRECT AND INDIRECT VIRAL INDUCED MUTATIONS




$P_1$ = provirus

$E_1$ = exons

$I_1$ = introns

vt'RNA = viral transfer-like RNA (e.g., EBER 1 and EBER 2 encoded by Epstein-Barr virus)

# *Preliophics – New Ways of Thinking and Novel Approaches to Science*

- Electrophoresis (e.g., Pauling and O'Farrell) versus preliophics (Smith and Shadel)
    - Electrophoresis is useful in elucidating and explicating molecular ***structure***
    - Preliophics is useful in elucidating and explicating molecular ***function***
- Anticipatory and Logistic reasoning

# *Logistic Reasoning and Anticipatory Sciences*

The concept of logistic reasoning was introduced in 1983 in response to perceived inadequacies in critical reasoning skills in life and information sciences (Smith, 1983). Logistic reasoning (LR) is a quasi-goal-oriented process involving asking "good" questions (i.e., question-asking involving 'why', 'why not', 'what if', 'what is taught or learned', and 'what is anticipated or next') and 'question-answering'/problem-solving, 'look-ahead', fault and error analysis (including expectations of Murphy's Law; to wit, 'when something can go wrong, it may occur'), and erotetic logic – the logic and science of question-asking. Succinctly, LR is about seeing the 'big picture'. These processes are analogous to strategies used by systems designers, computer programmers, and chess and "Go" masters.

The processes go beyond classic *gedanken studies* (Smith, 1979; Smith, 1982; Smith, 1983; Smith, 2006; Smith, 2007; Smith, 2008; cf. Platt, 1964; Nersessian, 1992). In general, LR is concerned with how 'things' and systems work together (including broad concerns about 'common sense'; Smith, 2006c; Smith, 2007; Smith, 2008b), how they fail to work together, and discerning if and when they cannot work together.

An ultimate goal in LR is to see the 'biggest pictures' first, and then focus on the minutiae (i.e. to paraphrase an old saw, 'one should see the forest first, and then its trees', though also allowing for the forests to be illusory). By analogy, LR should function as a mental global positioning satellite system (GPSS) device insofar as, when kept up-to-date, it should be capable of understanding and interpreting directionality and avoiding misunderstandings and errors. LR should reveal an appreciation for the retrospective (both synchronic and diachronic issues), prospective and anticipatory (Smith, 2010; cf. Nadin, 1999). These often prove to be essential in characterizing feedforward, feedback and skip-ahead processes often associated with systems and processes.

A promising application of LR pertains to LR about molecular mimicry. One inference regarding autovirulence and molecular mimicry is that the products of molecular mimicry have consistent structures *and functions*. For example, α-interferons and acid-labile α-interferons should be consistent (respectively) and not vary in structure or function (or aberrant function) from one instance to another. Hence, high-speed computer techniques as well as preliophics may be useful in categorizing many of those consistent functions and aberrant functions. One example would be to circumscribe those aberrant translation products that possess mutagenic potential (Smith, 2010). This could have value in *anticipating*, treating, circumventing and preventing cancers and other diseases (e.g., TNR diseases).

The application of LR in the explication of molecular mimicry vis-à-vis autism spectrum disorders, schizophrenia and other mental disorders may have even greater significance. It could lead to approaches for identifying, assessing and resolving signal and noise issues; to wit, disambiguating signals (e.g., genes and gene products) versus noises (e.g., discoveries of *de novo* mutations, and broad and enigmatic psychiatric clinical symptoms) associated with scientific, transdisciplinary and professional terrain.

These signal-to-noise issues could represent the unspoken and unforeseen basis of the “unnecessary battle” among neuroscientists and geneticists regarding the biology of mental disorders (Editorial, 2008; cf. Abbott, 2008). Perhaps most important, an appreciation of functional products (and properties) of molecular mimicry could have long-term value in elucidating issues such as aberrant “beliefs,” “awareness,” “realities,” “savantism,” and diverse (albeit concrete) symptoms in other neuropsychiatric disorders such as hallucinations, paranoia, coprolalia, tics, delusions, obsessions, compulsions, dissociative behavior, etc. Concretely, analyses of products of molecular mimicry may provide insights into receptors and their agonists and antagonists. Those analyses also may clarify whether the salutary effects of psychoactive drugs derive from interactions with normal or aberrant molecular byproducts.

Overall, an aim in LR is to give concrete meaning to Louis Pasteur’s quote in a 1854 lecture at the University of Lille; to wit, “in the field of observation, chance favors the prepared mind.”

# *Normal versus Aberrant Molecular Function*

**Schematic of Normal Molecular Chemistry.** In general, X and Y are gene-encoded molecules

$X_1 + Y_1 \rightarrow Z_1$ ~ non-symptomatic normal molecular function
$X_2 + Y_2 \rightarrow Z_2$ ~ non-symptomatic normal molecular function
$X_3 + Y_3 \rightarrow Z_3$ ~ non-symptomatic normal molecular function
**…**
$X_n + Y_n \rightarrow Z_n$ ~ non-symptomatic normal molecular function

**Schematic of Aberrant Molecular Chemistry**. In general, X, and Y are normal gene-encoded molecules; and, X*, Y* and/or Z* are aberrant epigenetic molecules.

$X^*_1 + Y_1 \rightarrow Z^*_1$ ~ * associated with discrete symptoms, conditions and outcomes-1'
$X^*_2 + Y_2 \rightarrow Z^*_2$ ~ * associated with discrete symptoms, conditions and outcomes-2'
$X^*_3 + Y_3 \rightarrow Z^*_3$ ~ * associated with discrete symptoms, conditions and outcomes-3'
**…**
$X^*_n + Y^*_n \rightarrow Z^*_n$ ~ * associated with discrete symptoms, conditions and outcomes-n'

**Alternative Schematic of Aberrant Molecular Chemistry**. In general, X, and Y are normal gene-encoded molecules; and, X*, Y* and/or Z* are aberrant epigenetic molecules.

$X_1 + Y^*_1 \rightarrow Z^*_1$ ~ * associated with discrete symptoms, conditions and outcomes-1"
$X_2 + Y^*_2 \rightarrow Z^*_2$ ~ * associated with discrete symptoms, conditions and outcomes-2"
$X_3 + Y^*_3 \rightarrow Z^*_3$ ~ * associated with discrete symptoms, conditions and outcomes-3"
**…**
$X_n + Y^*_n \rightarrow Z^*_n$ ~ * associated with discrete symptoms, conditions and outcomes-n"

**Another Schematic of Aberrant Molecular Chemistry**. In general, X, and Y are normal gene-encoded molecules; and, X*, Y* and/or Z** are aberrant epigenetic molecules.

$X^*_1 + Y^*_1 \rightarrow Z^{**}_1$ ~** associated with discrete symptoms, conditions and outcomes-1º
$X^*_2 + Y^*_2 \rightarrow Z^{**}_2$ ~** associated with discrete symptoms, conditions and outcomes-2º
$X^*_3 + Y^*_3 \rightarrow Z^{**}_3$ ~** associated with discrete symptoms, conditions and outcomes-3º
**…**
$X^*_n + Y^*_n \rightarrow Z^{**}_n$ ~** associated with discrete symptoms, conditions and outcomes-nº

## *Notes on the previous slides pertaining to normal and aberrant molecular functions*

- There may be no gene for the aberrant molecular moieties and species. Rather, autovirulent actions may produce some consistent epigenetic molecular byproducts. It now is important to explicate and elucidate those consistent aberrant actions.
- Traditional notions of epigenetics (e.g., methylations) must be revised to reflect real or potential aberrations in molecular byproducts (cf. Smith, 2003b).
- Autovirulence is a significant contributor to evolution as environmental generators of diversity and/or congenital generators of conditions and alternative life-styles.
- Smith's tripartite model of evolution comports with data on evolution more than classic Darwinian and Lamarckian theories (Smith, 2006).
- Fault and error analyses provide substantial evidence supporting DNA as the repository of long-term memory in all organ and developmental systems.
- These findings support autotoxicity, autovirulence and context-specificity as a general theory of aberrations, faults, errors and stress-induced evolutionary outcomes.
- Preliophic moleculators and preliophic processes may be essential in disambiguating causality, aberrant (epigenetic) molecular functions *whereas electrophoresis has no application* (cf. Pauling et al., 1949).
- Preliophic devices and processes could explicate each of the chemical equations.
- Sequences 2 … n could represent *a posteriori* downstream consequences of some initial (#1) *a priori* aberrant event. Each precise molecular event could be investigated using preliophic devices and/or processes.
- Revisions in nomenclature now may be exceedingly important. Just as most scholars now will agree that homosexuality is not a disorder or disease, consequences of aberrant epigenetic actions may represent conditions and/or outcomes. Savantism in some autism spectrum disorders is one such example. The so-called Mongoloid facial features in Down syndrome may be another example.
- The no-fault, blame-free professional management of stress (e.g., by physicians, other clinicians, spiritualists, educators et al.) may represent the most important intervention and consequence of the theory of autovirulence (cf, Sabatier, 1988).

# Sickle Cell Anemia, a Molecular Disease[1]

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*Gates and Crellin Laboratories of Chemistry,*
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THE ERYTHROCYTES of certain individuals possess the capacity to undergo reversible changes in shape in response to changes in the partial pressure of oxygen. When the oxygen pressure is lowered, these cells change their forms from the normal biconcave disk to crescent, holly wreath, and other forms. This process is known as sickling. About 8 percent of American Negroes possess this characteristic; usually they exhibit no pathological consequences ascribable to it. These people are said to have sicklemia, or sickle cell trait. However, about 1 in 40 (*4*) of these individuals whose cells are capable of sickling suffer from a severe chronic anemia resulting from excessive destruction of their erythrocytes; the term sickle cell anemia is applied to their condition.

The main observable difference between the erythrocytes of sickle cell trait and sickle cell anemia has been that a considerably greater reduction in the partial pressure of oxygen is required for a major fraction of the trait cells to sickle than for the anemia cells (*11*). Tests *in vivo* have demonstrated that between 30 and 60 percent of the erythrocytes in the venous circulation of sickle cell anemic individuals, but less than 1 percent of those in the venous circulation of sicklemic individuals, are normally sickled. Experiments *in vitro* indicate that under sufficiently low oxygen pressure, however, all the cells of both types assume the sickled form.

The evidence available at the time that our investigation was begun indicated that the process of sickling might be intimately associated with the state and the nature of the hemoglobin within the erythrocyte. Sickle cell erythrocytes in which the hemoglobin is combined with oxygen or carbon monoxide have the biconcave disk contour and are indistinguishable in that form from normal erythrocytes. In this condition they are termed promeniscocytes. The hemoglobin appears to be uniformly distributed and randomly oriented within normal cells and promeniscocytes, and no birefringence is observed. Both types of cells are very flexible. If the oxygen or carbon monoxide is removed, however, transforming the hemoglobin to the uncombined state, the promeniscocytes undergo sickling. The hemoglobin within the sickled cells appears to aggregate into one or more foci, and the cell membranes collapse. The cells become birefringent (*11*) and quite rigid. The addition of oxygen or carbon monoxide to these cells reverses these phenomena. Thus the physical effects just described depend on the state of combination of the hemoglobin, and only secondarily, if at all, on the cell membrane. This conclusion is supported by the observation that sickled cells when lysed with water produce discoidal, rather than sickle-shaped, ghosts (*10*).

It was decided, therefore, to examine the physical and chemical properties of the hemoglobins of individuals with sicklemia and sickle cell anemia, and to compare them with the hemoglobin of normal individuals to determine whether any significant differences might be observed.

## Experimental Methods

The experimental work reported in this paper deals largely with an electrophoretic study of these hemoglobins. In the first phase of the investigation, which concerned the comparison of normal and sickle cell anemia hemoglobins, three types of experiments were performed: 1) with carbonmonoxyhemoglobins; 2) with uncombined ferrohemoglobins in the presence of dithionite ion, to prevent oxidation to methemoglobins; and 3) with carbonmonoxyhemoglobins in the presence of dithionite ion. The experiments of type 3 were performed and compared with those of type 1 in order to ascertain whether the dithionite ion itself causes any specific electrophoretic effect.

Samples of blood were obtained from sickle cell anemic individuals who had not been transfused within three months prior to the time of sampling. Stroma-free concentrated solutions of human adult hemoglobin were prepared by the method used by Drabkin (*3*). These solutions were diluted just before use with the

[1] This research was carried out with the aid of a grant from the United States Public Health Service. The authors are grateful to Professor Ray D. Owen, of the Biology Division of this Institute, for his helpful suggestions. We are indebted to Dr. Edward R. Evans, of Pasadena, Dr. Travis Winsor, of Los Angeles, and Dr. G. E. Burch, of the Tulane University School of Medicine, New Orleans, for their aid in obtaining the blood used in these experiments.

[2] U. S. Public Health Service postdoctoral fellow of the National Institutes of Health.

[3] Postdoctoral fellow of the Division of Medical Sciences of the National Research Council.

[4] Contribution No. 1333.

appropriate buffer until the hemoglobin concentrations were close to 0.5 grams per 100 milliliters, and then were dialyzed against large volumes of these buffers for 12 to 24 hours at 4° C. The buffers for the experiments of types 2 and 3 were prepared by adding 300 ml of 0.1 ionic strength sodium dithionite solution to 3.5 liters of 0.1 ionic strength buffer. About 100 ml of 0.1 molar NaOH was then added to bring the pH of the buffer back to its original value. Ferrohemoglobin solutions were prepared by diluting the concentrated solutions with this dithionite-containing buffer and dialyzing against it under a nitrogen atmosphere. The hemoglobin solutions for the experiments of type 3 were made up similarly, except that they were saturated with carbon monoxide after dilution and were dialyzed under a carbon monoxide atmosphere. The dialysis bags were kept in continuous motion in the buffers by means of a stirrer with a mercury seal to prevent the escape of the nitrogen and carbon monoxide gases.

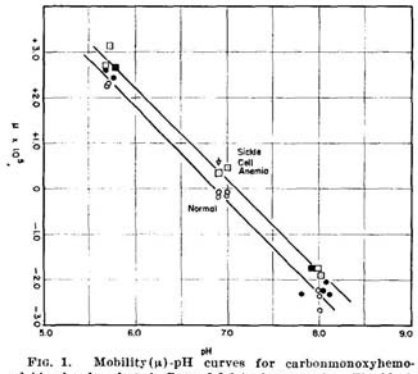


FIG. 1. Mobility(μ)-pH curves for carbonmonoxyhemoglobins in phosphate buffers of 0.1 ionic strength. The black circles and black squares denote the data for experiments performed with buffers containing dithionite ion. The open square designated by the arrow represents an average value of 10 experiments on the hemoglobin of different individuals with sickle cell anemia. The mobilities recorded in this graph are averages of the mobilities in the ascending and descending limbs.

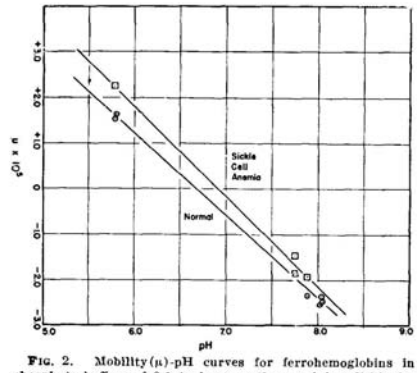


FIG. 2. Mobility(μ)-pH curves for ferrohemoglobins in phosphate buffers of 0.1 ionic strength containing dithionite ion. The mobilities recorded in the graph are averages of the mobilities in the ascending and descending limbs.

The experiments were carried out in the modified Tiselius electrophoresis apparatus described by Swingle (*14*). Potential gradients of 4.8 to 8.4 volts per centimeter were employed, and the duration of the runs varied from 6 to 20 hours. The pH values of the buffers were measured after dialysis on samples which had come to room temperature.

## RESULTS

The results indicate that a significant difference exists between the electrophoretic mobilities of hemoglobin derived from erythrocytes of normal individuals and from those of sickle cell anemic individuals. The two types of hemoglobin are particularly easily distinguished as the carbonmonoxy compounds at pH 6.9 in phosphate buffer of 0.1 ionic strength. In this buffer the sickle cell anemia carbonmonoxyhemoglobin moves as a positive ion, while the normal compound moves as a negative ion, and there is no detectable amount of one type present in the other.[4] The hemoglobin derived from erythrocytes of individuals with sicklemia, however, appears to be a mixture of the normal hemoglobin and sickle cell anemia hemoglobin in roughly equal proportions. Up to the present time the hemoglobins of 15 persons with sickle cell anemia, 8 persons with sicklemia, and 7 normal adults have been examined. The hemoglobins of normal adult white and negro individuals were found to be indistinguishable.

The mobility data obtained in phosphate buffers of 0.1 ionic strength and various values of pH are summarized in Figs. 1 and 2.[5]

[4] Occasionally small amounts (less than 5 percent of the total protein) of material with mobilities different from that of either kind of hemoglobin were observed in these uncrystallized hemoglobin preparations. According to the observations of Stern, Reiner, and Silber (*12*) a small amount of a component with a mobility smaller than that of oxyhemoglobin is present in human erythrocyte hemolyzates.

[5] The results obtained with carbonmonoxyhemoglobins with and without dithionite ion in the buffers indicate that the dithionite ion plays no significant role in the electrophoretic properties of the proteins. It is therefore of interest that ferrohemoglobin was found to have a lower isoelectric point in phosphate buffer than carbonmonoxyhemoglobin. Titration studies have indicated (*5*, *6*) that oxyhemoglobin (similar in electrophoretic properties to the carbonmonoxy compound) has a lower isoelectric point than ferrohemoglobin in

The isoelectric points are listed in Table 1. These results prove that the electrophoretic difference between normal hemoglobin and sickle cell anemia hemoglobin

TABLE 1

ISOELECTRIC POINTS IN PHOSPHATE BUFFER, $\mu = 0.1$

| Compound | Normal | Sickle cell anemia | Difference |
|---|---|---|---|
| Carbonmonoxyhemoglobin | 6.87 | 7.09 | 0.22 |
| Ferrohemoglobin ..... | 6.87 | 7.09 | 0.22 |

exists in both ferrohemoglobin and carbonmonoxyhemoglobin. We have also performed several experiments in a buffer of 0.1 ionic strength and pH 6.52 containing 0.08 M NaCl, 0.02 M sodium cacodylate, and 0.0083 M cacodylic acid. In this buffer the average mobility of sickle cell anemia carbonmonoxyhemoglobin is $2.63 \times 10^{-5}$, and that of normal carbonmonoxyhemoglobin is $2.23 \times 10^{-5}$ cm/sec per volt/cm.[6]

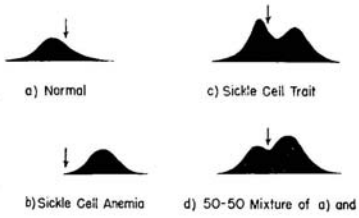


FIG. 3. Longsworth scanning diagrams of carbonmonoxyhemoglobins in phosphate buffer of 0.1 ionic strength and pH 6.90 taken after 20 hours' electrophoresis at a potential gradient of 4.73 volts/cm.

These experiments with a buffer quite different from phosphate buffer demonstrate that the difference between the hemoglobins is essentially independent of the buffer ions.

Typical Longsworth scanning diagrams of experiments with normal, sickle cell anemia, and sicklemia carbonmonoxyhemoglobins, and with a mixture of the first two compounds, all in phosphate buffer of pH 6.90 and ionic strength 0.1, are reproduced in Fig. 3. It is apparent from this figure that the sicklemia material contains less than 50 percent of the anemia component. In order to determine this quantity accurately some experiments at a total protein concentration of 1 percent were performed with known mixtures of sickle cell anemia and normal carbonmonoxyhemoglobins in the cacodylate-sodium chloride buffer of 0.1 ionic strength and pH 6.52 described above. This buffer was chosen in order to minimize the anomalous electrophoretic effects observed in phosphate buffers (*7*). Since the two hemoglobins were incompletely resolved after 15 hours of electrophoresis under a potential gradient of 2.79 volts/cm, the method of Tiselius and Kabat (*16*) was employed to allocate the

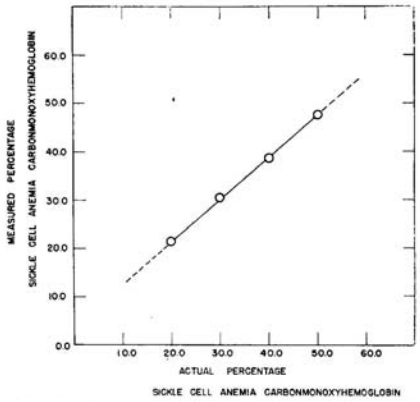


FIG. 4. The determination of the percent of sickle cell anemia carbonmonoxyhemoglobin in known mixtures of the protein with normal carbonmonoxyhemoglobin by means of electrophoretic analysis. The experiments were performed in a cacodylate sodium chloride buffer described in the text.

areas under the peaks in the electrophoresis diagrams to the two components. In Fig. 4 there is plotted the percent of the anemia component calculated from the areas so obtained against the percent of that component in the known mixtures. Similar experiments were performed with a solution in which the hemoglobins of 5 sicklemic individuals were pooled. The relative concentrations of the two hemoglobins were calculated from the electrophoresis diagrams, and the actual proportions were then determined from the plot of Fig. 4. A value of 39 percent for the amount of the sickle cell anemia component in the sicklemia hemoglobin was arrived at in this manner. From the experiments we have performed thus far it appears that this value does not vary greatly from one sicklemic individual to another, but a more extensive study of this point is required.

Up to this stage we have assumed that one of the two components of sicklemia hemoglobin is identical with sickle cell anemia hemoglobin and the other is identical with the normal compound. Aside from the

the absence of other ions. These results might be reconciled by assuming that the ferrous iron of ferrohemoglobin forms complexes with phosphate ions which cannot be formed when the iron is combined with oxygen or carbon monoxide. We propose to continue the study of this phenomenon.

[6] The mobility data show that in 0.1 ionic strength cacodylate buffers the isoelectric points of the hemoglobins are increased about 0.5 pH unit over their values in 0.1 ionic strength phosphate buffers. This effect is similar to that observed by Longsworth in his study of ovalbumin (*7*).

genetic evidence which makes this assumption very probable (see the discussion section), electrophoresis experiments afford direct evidence that the assumption is valid. The experiments on the pooled sicklemia carbonmonoxyhemoglobin and the mixture containing 40 percent sickle cell anemia carbonmonoxyhemoglobin and 60 percent normal carbonmonoxyhemoglobin in the cacodylate-sodium chloride buffer described above were compared, and it was found that the mobilities of the respective components were essentially identical.[7] Furthermore, we have performed experiments in which normal hemoglobin was added to a sicklemia preparation and the mixture was then subjected to electrophoretic analysis. Upon examining the Longsworth scanning diagrams we found that the area under the peak corresponding to the normal component had increased by the amount expected, and that no indication of a new component could be discerned. Similar experiments on mixtures of sickle cell anemia hemoglobin and sicklemia preparations yielded similar results. These sensitive tests reveal that, at least electrophoretically, the two components in sicklemia hemoglobin are identifiable with sickle cell anemia hemoglobin and normal hemoglobin.

## Discussion

1) *On the Nature of the Difference between Sickle Cell Anemia Hemoglobin and Normal Hemoglobin*: Having found that the electrophoretic mobilities of sickle cell anemia hemoglobin and normal hemoglobin differ, we are left with the considerable problem of locating the cause of the difference. It is impossible to ascribe the difference to dissimilarities in the particle weights or shapes of the two hemoglobins in solution: a purely frictional effect would cause one species to move more slowly than the other throughout the entire pH range and would not produce a shift in the isoelectric point. Moreover, preliminary velocity ultracentrifuge[8] and free diffusion measurements indicate that the two hemoglobins have the same sedimentation and diffusion constants.

The most plausible hypothesis is that there is a difference in the number or kind of ionizable groups in the two hemoglobins. Let us assume that the only groups capable of forming ions which are present in carbonmonoxyhemoglobin are the carboxyl groups in the heme, and the carboxyl, imidazole, amino, phenolic hydroxyl, and guanidino groups in the globin. The number of ions nonspecifically adsorbed on the two proteins should be the same for the two hemoglobins under comparable conditions, and they may be neglected for our purposes. Our experiments indicate that the net number of positive charges (the total number of cationic groups minus the number of anionic groups) is greater for sickle cell anemia hemoglobin than for normal hemoglobin in the pH region near their isoelectric points.

According to titration data obtained by us, the acid-base titration curve of normal human carbonmonoxyhemoglobin is nearly linear in the neighborhood of the isoelectric point of the protein, and a change of one pH unit in the hemoglobin solution in this region is associated with a change in net charge on the hemoglobin molecule of about 13 charges per molecule. The same value was obtained by German and Wyman (*5*) with horse oxyhemoglobin. The difference in isoelectric points of the two hemoglobins under the conditions of our experiments is 0.23 for ferrohemoglobin and 0.22 for the carbonmonoxy compound. This difference corresponds to about 3 charges per molecule. With consideration of our experimental error, sickle cell anemia hemoglobin therefore has 2–4 more net positive charges per molecule than normal hemoglobin.

Studies have been initiated to elucidate the nature of this charge difference more precisely. Samples of porphyrin dimethyl esters have been prepared from normal hemoglobin and sickle cell anemia hemoglobin. These samples were shown to be identical by their x-ray powder photographs and by identity of their melting points and mixed melting point. A sample made from sicklemia hemoglobin was also found to have the same melting point. It is accordingly probable that normal and sickle cell anemia hemoglobin have different globins. Titration studies and amino acid analyses on the hemoglobins are also in progress.

2) *On the Nature of the Sickling Process*: In the introductory paragraphs we outlined the evidence which suggested that the hemoglobins in sickle cell anemia and sicklemia erythrocytes might be responsible for the sickling process. The fact that the hemoglobins in these cells have now been found to be different from that present in normal red blood cells makes it appear very probable that this is indeed so.

We can picture the mechanism of the sickling process in the following way. It is likely that it is the globins rather than the hemes of the two hemoglobins that are different. Let us propose that there is a surface region on the globin of the sickle cell anemia, hemoglobin molecule which is absent in the normal molecule and which has a configuration complementary to a different region of the surface of the hemoglobin molecule. This situation would be somewhat analogous to that which very probably exists in antigen-antibody reactions (*9*). The fact that sick-

[7] The patterns were very slightly different in that the known mixture contained 1 percent more of the sickle cell anemia component than did the sickle cell trait material.

[8] We are indebted to Dr. M. Moskowitz, of the Chemistry Department, University of California at Berkeley, for performing the ultracentrifuge experiments for us.

ling occurs only when the partial pressures of oxygen and carbon monoxide are low suggests that one of these sites is very near to the iron atom of one or more of the hemes, and that when the iron atom is combined with either one of these gases, the complementariness of the two structures is considerably diminished. Under the appropriate conditions, then, the sickle cell anemia hemoglobin molecules might be capable of interacting with one another at these sites sufficiently to cause at least a partial alignment of the molecules within the cell, resulting in the erythrocyte's becoming birefringent, and the cell membrane's being distorted to accommodate the now relatively rigid structures within its confines. The addition of oxygen or carbon monoxide to the cell might reverse these effects by disrupting some of the weak bonds between the hemoglobin molecules in favor of the bonds formed between gas molecules and iron atoms of the hemes.

Since all sicklemia erythrocytes behave more or less similarly, and all sickle at a sufficiently low oxygen pressure (*11*), it appears quite certain that normal hemoglobin and sickle cell anemia hemoglobin coexist within each sicklemia cell; otherwise there would be a mixture of normal and sickle cell anemia erythrocytes in sicklemia blood. We might expect that the normal hemoglobin molecules, lacking at least one type of complementary site present on the sickle cell anemia molecules, and so being incapable of entering into the chains or three-dimensional frameworks formed by the latter, would interfere with the alignment of these molecules within the sicklemia erythrocyte. Lower oxygen pressures, freeing more of the complementary sites near the hemes, might be required before sufficiently large aggregates of sickle cell anemia hemoglobin molecules could form to cause sickling of the erythrocytes.

This is in accord with the observations of Sherman (*11*), which were mentioned in the introduction, that a large proportion of erythrocytes in the venous circulation of persons with sickle cell anemia are sickled, but that very few have assumed the sickle forms in the venous circulation of individuals with sicklemia. Presumably, then, the sickled cells in the blood of persons with sickle cell anemia cause thromboses, and their increased fragility exposes them to the action of reticulo-endothelial cells which break them down, resulting in the anemia (*1*).

It appears, therefore, that while some of the details of this picture of the sickling process are as yet conjectural, the proposed mechanism is consistent with experimental observations at hand and offers a chemical and physical basis for many of them. Furthermore, if it is correct, it supplies a direct link between the existence of "defective" hemoglobin molecules and the pathological consequences of sickle cell disease.

3) *On the Genetics of Sickle Cell Disease*: A genetic basis for the capacity of erythrocytes to sickle was recognized early in the study of this disease (*4*). Taliaferro and Huck (*15*) suggested that a single dominant gene was involved, but the distinction between sicklemia and sickle cell anemia was not clearly understood at the time. The literature contains conflicting statements concerning the nature of the genetic mechanisms involved, but recently Neel (*8*) has reported an investigation which strongly indicates that the gene responsible for the sickling characteristic is in heterozygous condition in individuals with sicklemia, and homozygous in those with sickle cell anemia.

Our results had caused us to draw this inference before Neel's paper was published. The existence of normal hemoglobin and sickle cell anemia hemoglobin in roughly equal proportions in sicklemia hemoglobin preparations is obviously in complete accord with this hypothesis. In fact, if the mechanism proposed above to account for the sickling process is correct, we can identify the gene responsible for the sickling process with one of an alternative pair of alleles capable through some series of reactions of introducing the modification into the hemoglobin molecule that distinguishes sickle cell anemia hemoglobin from the normal protein.

The results of our investigation are compatible with a direct quantitative effect of this gene pair; in the chromosomes of a single nucleus of a normal adult somatic cell there is a complete absence of the sickle cell gene, while two doses of its allele are present; in the sicklemia somatic cell there exists one dose of each allele; and in the sickle cell anemia somatic cell there are two doses of the sickle cell gene, and a complete absence of its normal allele. Correspondingly, the erythrocytes of these individuals contain 100 percent normal hemoglobin, 40 percent sickle cell anemia hemoglobin and 60 percent normal hemoglobin, and 100 percent sickle cell anemia hemoglobin, respectively. This investigation reveals, therefore, a clear case of a change produced in a protein molecule by an allelic change in a single gene involved in synthesis.

The fact that sicklemia erythrocytes contain the two hemoglobins in the ratio 40 : 60 rather than 50 : 50 might be accounted for by a number of hypothetical schemes. For example, the two genes might compete for a common substrate in the synthesis of two different enzymes essential to the production of the two different hemoglobins. In this reaction, the sickle cell gene would be less efficient than its normal allele. Or, competition for a common substrate might occur at some later stage in the series of reactions leading to the synthesis of the two hemoglobins. Mechanisms of this sort are discussed in more elaborate detail by Stern (*13*).

The results obtained in the present study suggest that the erythrocytes of other hereditary hemolytic anemias be examined for the presence of abnormal hemoglobins. This we propose to do.

*Based on a paper presented at the meeting of the National Academy of Sciences in Washington, D. C., in April, 1949, and at the meeting of the American Society of Biological Chemists in Detroit in April, 1949.*

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(12) **United States Patent**
**Smith et al.**

(10) **Patent No.: US 7,826,974 B2**
(45) **Date of Patent: Nov. 2, 2010**

(54) **PRELIOPHIC MOLECULATOR USING ELECTRIC FIELDS AND GRADIENTS FOR MANIPULATING MOLECULES**

(76) Inventors: **Roulette W. Smith**, P.O. Box 19061, Stanford, CA (US) 94309-9061; **Robert R. Shadel**, 1616 Church St., San Francisco, CA (US) 94131

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 61 days.

(21) Appl. No.: **10/879,627**

(22) Filed: **Jun. 29, 2004**

(65) **Prior Publication Data**

US 2005/0284760 A1 Dec. 29, 2005

(51) **Int. Cl.**

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|---|---|
| ***G01N 33/48*** | (2006.01) |
| *C12M 1/00* | (2006.01) |
| *G01N 31/00* | (2006.01) |
| *G06G 7/48* | (2006.01) |

(52) **U.S. Cl.** ..... **702/19**; 702/22; 703/11; 435/283.1

(58) **Field of Classification Search** ..... 702/19, 702/20; 435/6; 204/299

See application file for complete search history.

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*Primary Examiner*—Eric S Dejong

(57) **ABSTRACT**

Apparatus and methods of using the apparatus for inducing movement and interaction of molecules in an electric field of an electrophoretic device that is circular in configuration to mimic a living cell. The circular electrophoretic device supports an isoelectric focusing medium, such as a gel on a gel plate with one charged circular pole at the center and an oppositely charged concentric pole at the perimeter of the plate whereupon molecular substances having electronegative or electropositive charges placed in the gel will tend to migrate toward the oppositely charged pole to their isoelectric points, allowing researchers to devise experiments with multiple substances to track pathways of interaction during osmotic diffusion and polar directed migration through the medium that parallel pathways in a biological cell, the device having a thermal control for regulating the temperature of the analytical experiments using the device.

**24 Claims, 5 Drawing Sheets**

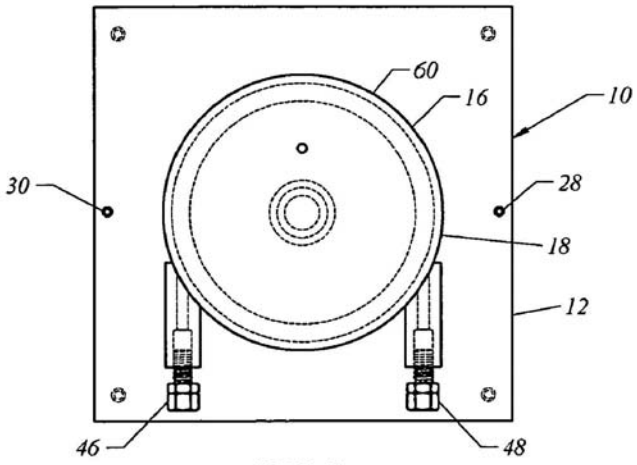


FIG. 1

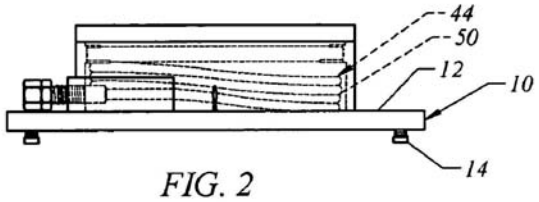


FIG. 2

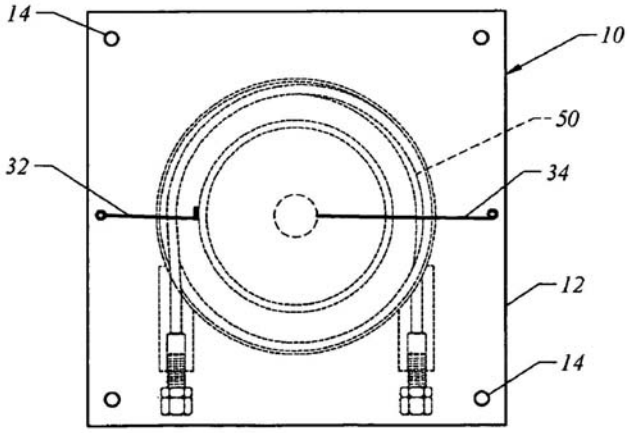


FIG. 3

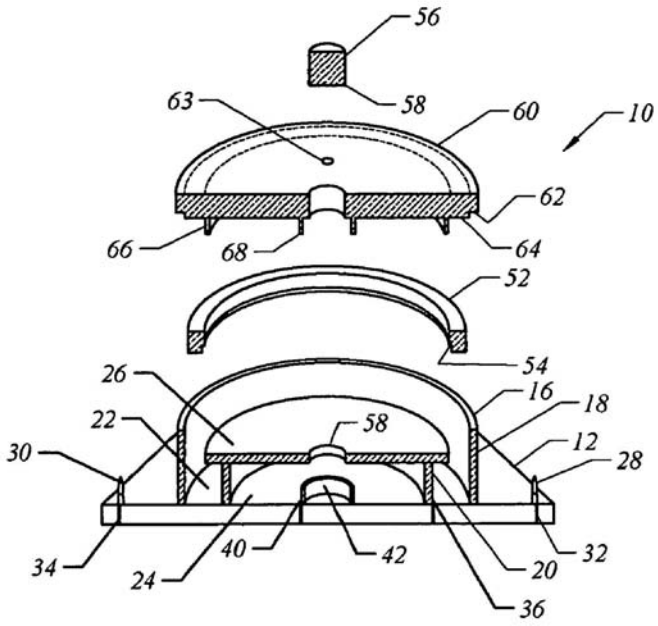
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FIG. 4

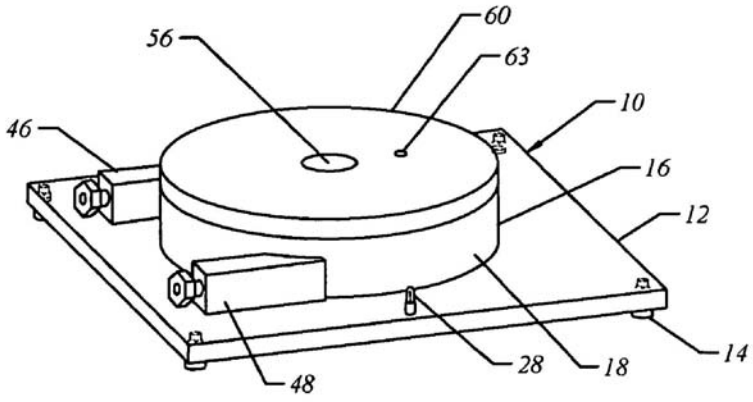
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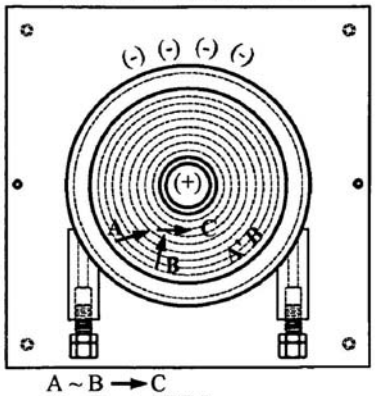
FIG. 5

PRELIOPHIC MOLECULATION PROCESSES

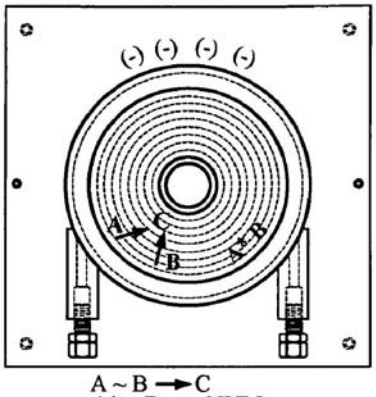
MOLECULAR MIMICRY




A ~ B → C
A' ~ B → NULL
A' IS ABERRANT TRASLATION PRODUCT OF A

*FIG. X1*

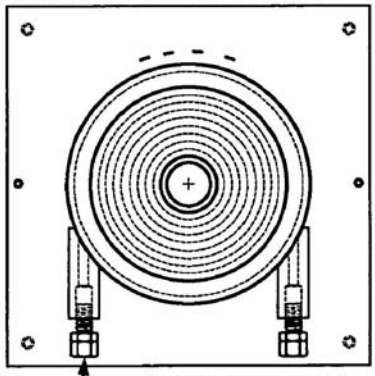
MOLECULAR CHIRALITY




A ~ B → C
A* ~ B → NULL
A* CHIRAL OPPOSITE OF A

*FIG. X2*

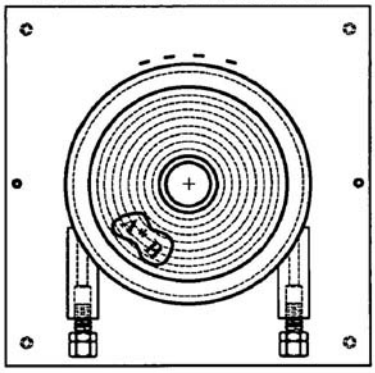
MOLECULAR EMULATION OF WARM AND COLD BLOOD




INPUT TEMPERATURE REGULATED TO BE CONSTANT VERSUS INPUT TEMPERATURE IS COLD OR VARIABLE

*FIG. X7*

JUST NOTICEABLE DIFFERENCE PHENOMENA




A ~ B ARE REAGENTS WITHIN A "JUST NOTICEABLE" DISTANCE - THE DEVICE AND PROCESS CAPTURE INTERACTIONS AS FUZZY AND ACCURATE PROCESSES

*FIG. X8*

PRELIOPHIC MOLECULATION PROCESSES

CELLULAR
MOLECULAR MICROGEOGRAPHY

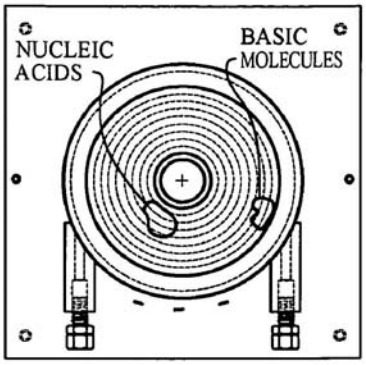



*FIG. X3*

CELLULAR
MOLECULAR MICROGEOGRAPHY

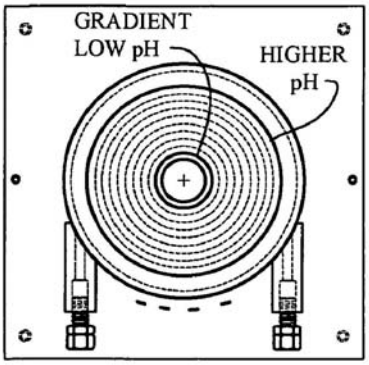
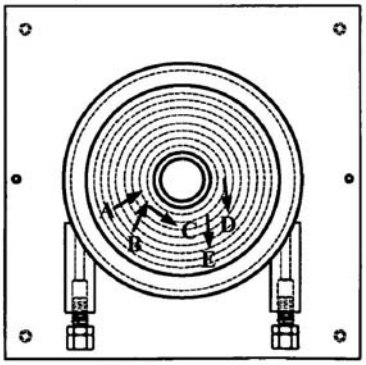



*FIG. X4*

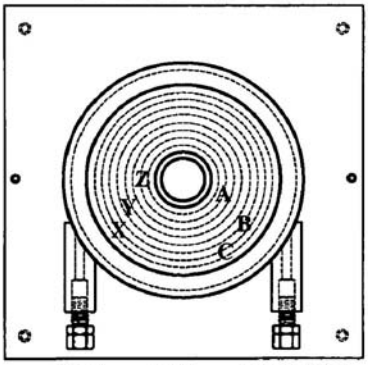
MOLECULAR COMPUTATION
(MOLECULATION)




A ~ B → C
C ~ D → E

*FIG. X5*

MOLECULAR MEMORY
VERSUS
CENTRAL DOGMA



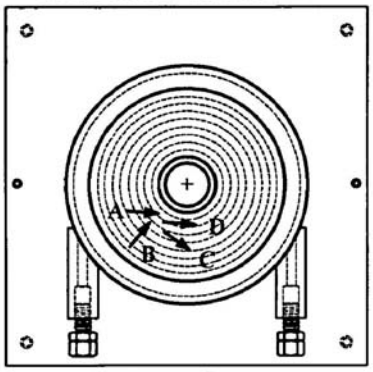

DNA RNA PROTEINS
A → B → C
(CENTRAL DOGMA)

CONFORMED MOLECULE → RNA INTERMEDIATE → DNA
X → Y → Z
(MEMORY - INVERSE PATHWAY)

*FIG. X6*

PROTOTYPICAL MOLECULATION PROCESSES

CONVERSION OF PROINSULIN TO INSULIN



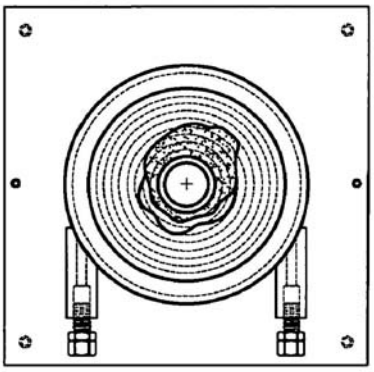

A ~ B → C, D

A= PROINSULIN C= INSULIN

B= TRYPSIN D= C-REACTIVE PEPTIDE

*FIG. X9*

MICROGEOGRAPHY

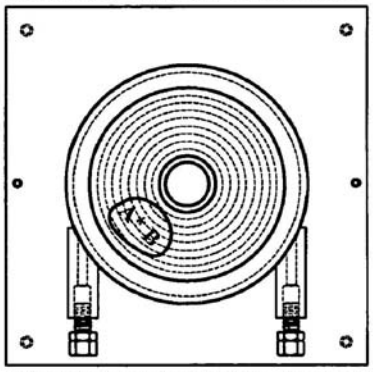


D= DNA

SHADED AREA REPRESENTS NUCLEUS AND HIGHLY ACIDIC ENVIRONMENT

*FIG. X10*

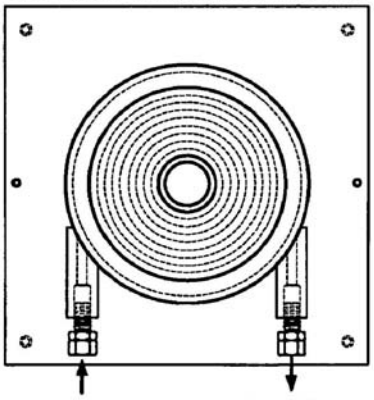
"JUST NOTICEABLE" CHEMISTRY




JUST NOTICEABLE DIFFERENCES BETWEEN MOLECULES PERMITS VISUALIZATION OF BIOCHEMICAL REACTION IN ENVIRONMENT ANALOGOUS TO IN VIVO ENVIRONMENT

*FIG. X11*

VARIABLE TEMPERATURE INPUT



OUTPUT

TO UNDERSTAND "COLD BLOODED" CHEMISTRY

*FIG. X12*

# PRELIOPHIC MOLECULATOR USING ELECTRIC FIELDS AND GRADIENTS FOR MANIPULATING MOLECULES

## BACKGROUND OF THE INVENTION

This invention is termed a preliophic moleculator and process for moleculation as an abbreviated terminology for a protonic-electronic-ionic-photonic molecular computer. Preliophic is derived from the first two letters of words in the hyphenated description along with the last "ic", thereby creating the coined term. The preliophic molecular computer is a device used to manipulate the motion and interaction of selected molecules in a medium (e.g., polyacrylamide, agarose or starch gel) under the influence of an electric field, induced pH gradient, or by some other means. The device and process are invented to mimic features of inferred interactions of molecules in cellular structures. However, it is expected that the physical device has application beyond experimental studies in molecular and cell biology, and in producing molecular byproducts. It will comprise a useful tool in all fields of chemistry, including theoretical, conceptual, logical and mathematical studies involving molecular interactions in a controlled environment. Indeed, the conceptual embodiment of the physical device and process are central elements in several derivative novel, logical, albeit counterintuitive (i.e., non-obvious) claims. These include: vaccines for use in acquired immunodeficiency syndrome (AIDS) and other lentivirus-related infections involving single or multivalent killed vaccines against relatively uncommon pathogens, though not against the lentiviruses themselves; devices used in elucidating "autotoxicity," "autovirulence," and "context specificity"; conceptualizing a gedanken study designed to reveal both changes in DNA in brain and measure changing G*C::A*T ratios using single-nucleotide polymorphism (SNP) analyses involving DNA extracted from cells in a hair follicle and three sections in brain; and, non-invasive methods, approaches and technologies for measuring nurture quantitatively, in both living and artificial environments, by using G*C::A*T ratios. Each of these corollary inventions is claimed in this patent application.

Molecular interactions produced in preliophic moleculation processes and devices are a direct contrast to the lack of molecular interactions in electrophoresis and electrophoresis devices. That is, electrophoresis (in contrast to preliophic moleculation) facilitates parallel movements of molecules which, by definition of parallelism, cannot interact. Thus, the preliophic moleculator and its processes are useful in elucidating and disambiguating molecular function, whereas electrophoresis is useful in elucidating molecular structure.

Typically, the medium used with the preliophic moleculator device and process is a gel or substrate similar to types used in electrophoresis devices and processes, and especially medium used in isoelectric focusing (IEF). However, it is expected that other non-gel mediums also may prove useful (e.g., viscous fluids, polyacrylamides, or other compositions through which intact, non-denatured molecules are able to migrate under the influence of electric fields or gradients). In this description such substances are termed substrate mediums. (NB: Throughout this description, the term "mediums" deliberately is used as the plural of medium, to distinguish mediums from media.)

The impetus for this invention is a series of discoveries and inferences suggesting that parsimony exists among most, if not all, molecular mechanisms of long-term memories (LTM) in living systems accounting for evolution, speciation, development, differentiation, immunity, cognition and behavior, aging, and death. Central to that parsimony are changes in DNA, claims to the contrary notwithstanding. As examples, it generally is agreed that "selection" among random changes in DNA is a basis of Darwinian evolution. Barbara McClintock generally is credited with demonstrating that changes in DNA (dubbed transpositions or "transposons") account for the developmental process producing variegation in maize. Other changes in and to DNA (including methylation) are associated with development and differentiation from singular cell to multiple cell organisms. Susumu Tonegawa demonstrated that rearrangements in DNA are central to immune memory and recognition. Compelling evidence now suggests that LTM in brain must involve a priori changes in DNA, especially in non-proteomic regions of the genome, with subsequent a posteriori generation and development of axons and dendrites in the neural network.



Changes in DNA in brain differ fundamentally from changes in DNA described by McClintock and Tonegawa insofar as changes in DNA in brain are not accompanied by cell division. Evolutionarily, it is thought that the bony cranium served to constrain or ablate cell division, while retaining molecular mechanisms for changing DNA especially in brain. Equally important, cell division in brain would be counterproductive because of the information redundancy. In other words, redundancy derived from cell division and clonal expansion in the immune system is desirable, whereas the lack of cellular redundancy (albeit with increased neuronal axon and dendrite connectivity) in brain, serves to facilitate molecular information processing in neurons. In the end, those DNA changes in brain are not heritable and/or transmitted to germline cells (e.g., sperm and ova) thereby differing from both Darwinian and Lamarckian evolution. Indeed, a major reason for inventing the preliophic device and process is to provide a concrete embodiment of an inverse to Francis Crick's "central dogma." According to the "central dogma" molecular information generally flows from DNA to RNA (by a process called transcription), and from RNA to proteins (by a process called translation). Crick subsequently allowed for "reverse transcription" after the discovery of retroviruses, yet it is noteworthy that the "central dogma" was flawed at the outset. For this thesis and invention to be viable, there are no "dogma" regarding movements of molecules into, within and out of living cells beyond being directed and vectorial, and in a manner that permits interactions among other directed and vectorial molecules.

Four key, albeit unreported and non-obvious, observations provided an additional logical basis for this invention. First, although there is a well established chemio-osmotic hypothesis for energy production and electron transfer within mitochondria in cells, a purpose for hydrogen ion (i.e., proton) byproducts pumped from mitochondria was never fully elaborated. Second, microheterogeneous commercial amphoteric molecules (i.e., "ampholytes") used in IEF and other electrophoretic processes are remarkably analogous to and concordant with the microheterogeneity in natural intercellular microtubulin-associated proteins (also known as "microtubule associated proteins," [MAPs]), and phosphatidyl-proteins and other phosphatidyl-moieties associated with cell membranes (e.g., phosphatidylserine, phosphatidylinositol, phosphatidylinesitol, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylethylamine). Third, the geometry of all electrophoretic devices, whether in one- or two-dimensional electrophoresis activities, is designed to examine and determine molecular structure based on parallel-movements of molecules in electric fields or proton gradients, with there being no potential for those devices to examine and determine molecular function. Structure is elucidated

because molecular species move in parallel, with molecular weight and charge often serving to define structure. Fourth, cellular histology, a vast variety of reported and unreported clinical, pathological and experimental findings, and preliminary experimentation, all point to the logic of a "molecular computer" based on molecules moving toward their isoelectric points (pI), though interacting with other molecules moving toward their isoelectric points.

The invention reported here is initially comprised of a circular device supporting a type of IEF medium, typically a gel with one charged pole in the center and an oppositely charged pole, comprises the entire perimeter of the device. For example, with a positive pole at the center and the perimeter serving as the negative pole, electronegatively charged molecules will move toward the center and electropositively charged molecules will move towards the cell boundary (i.e., perimeter). This is precisely as it happens in cells wherein basic molecules generally move toward the perimeter of the cell where the pH is approximately 7.4, and acidic molecules generally move toward the center of the cell where the pH can be as low as 2 to 3. Even without its actual construction, this conceptual embodiment of a preliophic moleculator now provides a conceptual basis for cellular micro-geography thereby providing logical and theoretical reasons for the nucleus generally being situated in the center of cells where pH values are low, and other cellular structures being distributed more peripherally in cells, regardless of cell shapes. (NB: The term pH is a designation for the percentage of hydrogen ions. Also noteworthy is that shapes other than circular shapes work equally well in this invention, including triangles, pie-shapes, etc.).

A temperature regulated system is incorporated in the device both to accommodate the dissipation of heat and to regulate the rate molecules may move in their directed pathways. Not only does the temperature regulated system obviate denaturing molecules, it facilitates modeling cold- versus warm-blooded molecular information processing.

The terms, "moleculator" and "moleculation" are used, respectively, to define the device and process for inducing the controlled migration of molecules in a substrate medium under the influence of an electric field, pH-gradient or other means. Implied in the terminology is the study of the interaction of migrating molecules, or molecules that approach or have reached their isoelectric location. Also implied in the terminology is the study of arbitrarily close interacting molecules, whether these interactions take place at some pH or otherwise.

The design of the device is particularly adapted for the study of biological functions and processes, as the circular configuration emulates the generally spherical configuration of the biological cell. Avenues for studying the dynamics involved in the progression or expression of disease also are provided by use of the moleculator device. For example, although rarely discussed and despite its ubiquity, the Epstein-Barr virus (EBV) is associated with more than 92 different diseases and syndromes, some of which involve "hit-and-run" and/or "beneath-the-radar" pathology. Many of these 92 diseases and syndromes mimic or comprise psychosomatic illnesses that often are stress-induced. The intriguing question was why would a common and ubiquitous virus be associated with such a wide variety of diseases and syndromes, yet almost never do more than two of these 92+ diseases or syndromes occur in the same person? What possible molecular mechanisms could account for this counter-intuitive finding and seeming conundrum? What theories and technologies could answer these questions?

The terms "autotoxicity," "autovirulence" and "context-specificity" were coined in 1983 to explain these and other phenomena, including prion-related diseases. A prototype of autovirulence is specifically implicated in stress-induced EBV-associated consequences in HIV and AIDS (e.g., dose-dependent production of acid-labile alpha-interferon). There was other evidence of EBV-induced aberrant translation products associated with the EBER I and EBER II small nuclear ribonucleoproteins (snRNPS) [RNA plus protein particles]. Other viruses and their snRNPs also could contribute to the production of aberrant translation products (e.g., snRNPs comprising VA I and VA II associated with some adenoviruses), whereas lentiviruses (e.g., HIV) are more likely to be associated with aberrant transcription products. Finally, it was noted that extant theories of autoimmune diseases (e.g., that the immune system is abnormally reacting to "self") could give way to novel possibilities that "self" or "abnormal-self" are abnormally presented to a healthy immune system, possibly involving "molecular mimicry" of "self." What remained was to invent an appropriate and practical technology to explicate these theories, findings and other phenomena.

Evidence of EBV-associated aberrant translation products in a variety of EBV-associated diseases and syndromes was reported. Inferential evidence suggests EBER I and/or EBER II contribute to aberrant translation products and molecular mimicry. The preliophic molecular of this invention is designed to study molecular function and infer molecular mimicry experimentally, even in the absence of precise details of amino-acid sequences, conformational variations and/or molecular mechanisms. It is suggested that the etiology of EBV-associated diseases and syndromes ultimately can be unraveled with the aid of the preliophic molecular.

It is noteworthy that preliophic moleculation is unlike electrophoresis in at least one very significant regard. As noted, electrophoresis provides a simple, excellent and economical approach for purifying structure. By way of contrast, arbitrarily complex functional systems can be elucidated and explicated using preliophic moleculators. For example, the molecular biology, genetics and genomics of long-term memory (LTM) in living systems can be studied using the preliophic moleculator of this invention, and in some instance providing logical or mathematical proofs, against claims to the contrary notwithstanding.

A 1979 review by one of the inventors of six decades of research on molecular bases of LTM in living systems supports changes in DNA as a priori bases for LTM in brain, with axon-dendrite connectivity representing a posteriori bases for neural networks. Furthermore, no models of LTM are mathematically or logically complete without affirming or rejecting the claim that "the definitive evaluation of DNA as the ultimate repository of information" in brain (Smith 1979). The 1979 review then cited six novel lines of inquiry supporting the DNA change hypothesis. Two decades later, research involving five of six lines of inquiry now provides further evidence supporting DNA changes as a basis of LTM. Insofar as the device is designed to emulate molecular information flow at the cellular level, the preliophic moleculator now provides a means to examine a corollary to the remaining line of inquiry. In the end, preliophic moleculation enables one to model changing G*C::A*T ratios over time, both experimentally and concretely. At a practical level, this line of inquiry also implicates host mechanisms contributing to the micro-heterogeneity in lentiviruses, thereby contributing to the "proof" that neutralizing vaccines cannot be produced against HIV or other lentiviruses; that is, the intrinsic unreliability of reverse transcriptases and host factors contribute to lentivirus

microheterogeneity. Inferentially, the conceptual embodiment of the preliophic moleculator reveals possibilities for non-invasive imaging technologies to model changing G*C::A*T ratios over time in intact cells and organisms, and in advanced preliophic devices. Such non-invasive imaging technologies most likely will focus on spin properties of phosphorus (in contrast to hydrogen) atoms in nuclear magnetic resonance studies.

If DNA in brain is subject to changes in association with LTM, it stands to reason that Francis Crick's "Central Dogma" of molecular biology is inadequate for explaining a necessary inverse flow of information possibly based on the input of conformational or other non-sequential representations of molecular information in contrast to sequential information embodied in the "central dogma." Interestingly, Crick may have anticipated this shortcoming given his little noted, albeit extraordinary, comment in a footnote: "There is, for example, the problem of the chemical nature of the agent of the disease scrapie." Nevertheless, we know enough to say that a non-trivial example showing that the classification was wrong could be an important discovery." This comment suggests a logical corollary about the flow of information in cells. Regardless, both pathways of information transfer [DNA to RNA to Proteins (connoted the "Central Dogma")] and an inverse pathway (conformational molecular information to endogenous- or exogenous-RNA-mediated reverse transcription (or other possible novel mechanisms) to changes in largely non-protein encoding regions of DNA) now can be studied in the invented preliophic moleculating device that emulates cellular molecular information processing (i.e., "moleculations"). Although there is not a Latinate term of art for this emulation process, preliophic molecular processes fall somewhere between being in vitro and in vivo. Indeed, preliophic moleculation, through its capture of functional molecular information processing, now makes it possible to educe mathematical and logical proofs that would not be possible in vivo and in vitro. The term "biological and chemical computability" is used to capture these logical and mathematical proofs, much akin and analogous to the notion of computability in computer sciences. The difference is that biological and chemical computability requires additional information about space, time, temperature and molecular vectorial positioning. As previously noted, this device and its moleculation processes also emulates artificial and cellular micro-geography positioned between in vivo and in vitro studies.

In the study of LTM and the evaluation of DNA as the ultimate repository of "information" (i.e., LTM) in the brain, the preliophic moleculator can aid in the empirical measurement and determination of DNA changes in the brain. The study of post-mortem brain tissue of exceptionally gifted individuals, descendants of such individuals at different ages, sets of identical twins raised together and apart, different sections of individual brains, and other such comparative studies, can be accomplished using the device of this invention. The potential for nuclear magnetic resonance studies already was cited. Use of fluorescent or other dyes also could find application, particularly in assessing changing G*C::A*T ratios.

Another complex conceptual embodiment of preliophic moleculation involves the study of causality in AIDS, and the formulation of vaccines for use in treating AIDS and other lentivirus infections. The former is mostly theoretical and inferential; the latter is largely empirical, though based on complex elements of the established cause. A brief sketch of the underlying reasoning follows.

Lentiviruses are one of three classes of retroviruses that produce changes in DNA when retrovirus RNA is "reverse transcribed" to form a DNA "provirus." A unique feature of lentiviruses—supported by a variety of clinical, experimental and epidemiological data—is that their proviruses generally occupy protected subclasses of cells in the immune system having LTM potential, which then are trans-activated by relatively uncommon nascent pathogens, though not relatively common pathogens. Other classes of retroviruses (i.e., oncoviruses and spumaviruses) generally lack trans-activation mechanisms, and generally do not occupy protected classes of immune system cells having LTM potential.

Although lentivirus trans-activation can be recursive in intact systems (i.e., lentiviruses can trans-activate themselves), lentivirus trans-activation most often is caused by relatively uncommon pathogens—so called opportunistic pathogens. Although distinctions between common and uncommon pathogens in AIDS have been known since the early 1980s, reasons for these distinctions remained elusive until the advent of conceptual preliophic moleculators.

Lentiviruses now provide a convenient means for highlighting several advanced preliophic moleculation applications possibly requiring multiple (and/or networked) preliophic devices. One application is to establish the cause of AIDS. To many scholars and investigators, HIV is the sine qua non for AIDS, whereas to others HIV may play no role in AIDS. Whether HIV is a necessary and sufficient element in AIDS, and the general matter of causality in AIDS has never been addressed; again, claims by O'Brien and Goedert (1996) to the contrary notwithstanding. Perhaps more broadly, are there necessary and sufficient rules or conditions required to establish causality in most infectious diseases? What roles can preliophic processes play in disambiguating these issues?

Among early attempts at defining conditions to establish causality are studies of anthrax by Robert Koch, based on work with his mentor, Jacob Henle. Koch formulated a set of postulates, often referred to as the Henle-Koch Postulates (HKP), which he used in demonstrating that *Bacillus anthracis* is indeed the cause of anthrax. Four elements are central to Koch's "proof." First the pathogen must be isolated from the intact organism. Second, the isolated pathogen must be inoculated into a single cell-type, which, in turn, produces characteristic pathological changes. Third, the isolated pathogen must be transmitted to an animal model, causing like disease. Fourth, once isolated again from the animal model, the pathogen must be inoculated in species from which it was first inoculated, and then shown to cause the same underlying disease. A critical theme in these postulates is that a single cell-type links the pathogen to the disease. An underlying axiom from sentential logic captures the spirit of these HKP; to with, Modus Penendo Ponens (if "A implies B" is true; and, if "A" is true; then, "B" is true). That is, if *Bacillus anthracis* causes anthrax is true; and, if *Bacillus anthracis* is the true pathogen associated with anthrax; then, anthrax can be inferred (to be the true consequence of *Bacillus anthracis*).

If HIV and other lentivirus infections are to be shown to be causes of AIDS or other diseases using HKP, a single cell-type must be associated with disease. Not only is this not true based on clinical, laboratory, experimental and epidemiological evidence, preliophic moleculators bring this into sharper focus. Multiple cell-types are associated with diseases caused by relatively uncommon (nascent) "opportunistic" pathogens that trans-activate the HIV (or other lentivirus) provirus in a separate cell-type. Advanced preliophic moleculation processes will emulate networks of multiple preliophic moleculators—one set perhaps to emulate the consequences of trans-

activation, and other sets perhaps to emulate associations between opportunistic pathogens and diseases.

Because HIV cannot be shown to be the sole or sufficient cause of AIDS using the HKP, what recourse is there? Proof lies in understanding distinctions between the effects of relatively common and uncommon pathogens in the HIV-infected individual (or in other lentivirus infections). There are compelling clinical, laboratory and epidemiological data that suggest that AIDS is not associated with relatively commonplace pathogens in HIV-infected persons. In short, a category of pathogens—so called relatively commonplace pathogens—do not play a role in trans-activating HIV. Indeed, considerable evidence suggests that the immune system remains intact for those pathogens. This finding can be emulated and modeled using preliophic moleculators, and give rise to applications of a second axiom from sentential logic; to wit, Modus Tollendo Tollens (if "A implies B" is true; and, if "not B" is true; then, "not A" is true). Modus Tollendo Tollens sometimes is referred to as "the rule of denial." Application of this axiom, when B comprises the relatively commonplace pathogens in an environment, confirms clinical, epidemiologic and laboratory findings; to wit, the cause of AIDS is HIV and selected relatively rare opportunistic pathogens. Although initially counterintuitive, an obvious corollary is that multivalent killed vaccines against relatively uncommon pathogens may circumvent trans-activation of HIV and other lentiviruses. This finding is affirmed in naturalistic studies involving Icelandic sheep between 1933 and 1954, simian AIDS-like diseases among primates in an animal colony at UC Davis during the late-1970s and mid-1980s, and in epidemiological data collected on human pathogens worldwide.

## SUMMARY OF THE INVENTION

The preliophic moleculator or moleculation device and the moleculation process of this invention are devised to aid in the study of arbitrarily complex biological and chemical processes. They are particularly useful in studies of molecular genetics, proteomics and genomics. They also find applications in elucidating and explicating infectious diseases involving extant infectious microbes (e.g., viruses and prions), as well as other novel infectious subparticles implicated in autotoxicity, autovirulence and context specificity. A conceptual embodiment of multiple (and possibly networked) preliophic moleculators, when coupled with sentential logic, allows one to identify the cause of AIDS by emulating roles of both HIV and selected opportunistic pathogens, and to infer and invent multivalent killed vaccines against relatively uncommon pathogens as vaccines against AIDS. These multivalent killed vaccines are non-obvious and counterintuitive insofar as they are not directed against HIV, though they circumscribe and circumvent lentivirus trans-activation.

The moleculation device of this invention includes (but is not limited to) a circular apparatus with a structure supporting and containing an IEF medium, typically a kind of gel used in electrophoresis. The IEF medium or substrate medium has an annular configuration contained by a central hub and a perimeter. Included in the structure at the central hub and perimeter in contact with the substrate medium are electrode poles having opposite charges. This arrangement creates a concentric array that mimics a biological cell. Unlike rectilinear electrophoretic analytic devices commonly utilized for molecular separations of compositions, the annular configuration divided into sectors provides opportunities for complex migrations with confluent mergers and collisional melding. By discrete placement of samples, osmotic diffusion as well as polar-directed migration is utilized in designing experimental processes.

The apparatus includes a cooling and temperature control system to both cool the substrate medium in a high voltage field and regulate the temperature of the substrate medium allowing experiments to be performed at different temperatures, for example, to simulate or emulate chemical processes in warm-blooded and cold-blooded animals. The cooling system includes a reservoir with a cooling coil having an external fluid input and output that is connectable to a fluid source such as a refrigerant or water supply.

With the exception of the poles and associated electronics, the apparatus is fabricated of a non-conductive material that does not chemically react with the reagents of the substrate medium or the substances being processed or analyzed. A clear plastic is preferred to allow observation of the substrate and cooling system to detect any reactions of visual interest or early manifestations of malfunction, particularly overheating. It is to be understood that the design of the apparatus described in this specification and shown in the drawings is a prototype for process experimentation, and, production units may differ in appearance, include minor changes or additions in function, and/or involve multiple networked units as in collections of cells comprising an organ or tissue.

The moleculation processes described in the specification are presented as examples of the process or method of moleculation using the unique type of apparatus described and are not intended to limit the scope or types of moleculation processes, both biological and chemical, intended to be covered by this specification. The process examples are conveniently described using a concentric array as a gradient overlay on a schematic representation of the apparatus and substrate. As noted, the concentric "bull's-eye" array may be divided into pie-shaped sectors for assisting in the setup and reporting of certain experiments. These and other features of the invention will become apparent from a consideration of the detailed description of the preferred embodiments.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a top view of the preliophic moleculator of this invention.

FIG. **2** is a side elevational view of the moleculator of FIG. **1**.

FIG. **3** is a bottom view of the moleculator of FIG. **1**.

FIG. **4** is a cross-sectional exploded view of the moleculator of FIG. **1**.

FIG. **5** is a perspective view of the moleculator of FIG. **1**.

FIGS. X**1**-X**12** are diagrammatic schematics illustrating process examples for the moleculator of this invention.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring to FIGS. **1**-**5**, the preliophic moleculator of this invention is designated generally by the reference numeral **10** and comprises a moleculation apparatus for experimental testing of the movement and interaction of molecules under the influence of an electrical field or induced gradient. The moleculation apparatus **10** includes a leveling base **12** with four corner leveling screws **14** that supports a circular containment structure **16**. The containment structure **16** includes a circular perimeter wall **18** that forms a buffer dam to contain the buffer liquid that is typically salt water. A circular inner wall **20** concentric to the perimeter wall **18** separates an outer buffer chamber **22** from an inner buffer chamber **24**. The inner

wall **20** also supports a stage **26** for the substrate medium, typically a gel that is either precast or preferably cast in place using the auxiliary components of the moleculation apparatus **10**.

Mounted on the leveling base **12** are two electrical terminals **28** and **30** which have separate conductors **32** and **34** running under the leveling base to wire electrodes **36** and **40** that respectively encircle the outside of the inner wall **20** and the outside of a concentric electrode mount **42**. The electrical terminals **28** and **30** are connected to female jacks (not shown) of a direct current power source to provide the voltage required to create the electric field desired. Typically the voltage is in the hundreds of volts and is a function of the mobility of the particular molecules under study, the medium selected and the time allotted. As expected higher voltage will accelerate molecular migrations.

In order to prevent overheating and maintain a desired temperature allowing consistency in experiments, a cooling system **44** is included in the apparatus **10**. The cooling system **44** includes an input connector **46** and an outflow connector **48** with a plastic cooling coil **50**, shown in dotted line in FIGS. **2** and **3**. The cooling coil **50** wraps around in the outer buffer chamber **24** and maintains the salt water buffer liquid at a desired temperature. It is to be understood that it is the substrate medium that is to be maintained at a desired temperature and that a system that maintained the substrate stage the desired temperature could be provided. In the system shown, by appropriately regulating the temperature of the cooling (or heating) water flowing through the coil **50**, the temperature of the buffer fluid and hence the substrate medium is controlled.

Where the substrate medium is not pre-cast, the moleculation apparatus **10** includes a removable gel cast ring **52** having an undercut notch **54** allowing the gel cast ring **52** to seat on the substrate medium stage **26**. Additionally, a center bung **56** with an undercut notch **58** is seated in a center hole **58** in the gel stage **26**. The ring **52** and bung **56** provide a dam for the heated gel when poured onto the stage **26**. Before the gel sets, a removable cover **60** having an undercut notch **62** and a vent hole **63** is seated on the perimeter wall **18**. On the underside **64** of the cover **60** are a circular outer projecting rim **66** and a circular concentric inner projecting hub **68** which hang into the forming gel without touching the stage **26**. When the gel sets, the cover **60**, bung **56** and ring **52** are removed leaving a cast gel with an inner and outer impression which provides concentric reservoirs (not shown) for samples. Notably, the cover **60**, which acts as a casting mold, can have a variety of different projecting elements configured for particular experiments. For example, the rim and hub can have a series of spaced notches which provide a series of spaced sample wells when the cover **60** is removed. After the samples are set according to the experiment contemplated, the substrate is filled before flooding. When operated, the buffer solution is raised over the substrate and the voltage is applied to the terminals. To protect a user from inadvertent electrical discharge and potentially hazardous shock, a plain cover without impression elements can be used during operation.

The moleculation apparatus **10** is fabricated from a clear plastic to permit observation of the migrations and reactions. Samples may be dyed to improve visualization. Electrodes are preferably platinum wire to resist corrosion but may be other corrosion resistant material and may be formed a ribbon.

Typically, the polarity of the electrodes is maintained with the outer electrode negative and the inner electrode positive. However, for a particular experiment it may be desirable to reverse the polarity with the outer electrode positive and the inner electrode negative. These and other modifications can be made to tailor the apparatus or alter the apparatus for a particular molecular manipulation.

FIGS. **X1** through **12** provide exemplars of the variety of different moleculations that are possible when using the moleculation apparatus as a molecular computer.

In FIG. **X1**, detection of molecular mimicry may be accomplished by a convergent migration of molecule A and reactant molecule B on a path where a reaction product C is generated, but the convergent migration of an aberrant translation product of A, being A' when merged with B does not generate a reaction product C.

Similarly, in FIG. **X2**, when detecting molecular chirality, reacting molecule A with reactant molecule B generates a detectable molecule C, but **A***, the chiral opposite of A generates null.

In FIG. **X3**, the moleculation apparatus is used to produce a micro geography of separated substances such as nucleic acids drawn to the positive electrode and basic molecules drawn to the negative electrode. Interaction could be determined by loading the substances at opposite poles with migration on a collision path for detection of reactivity before reaching their natural micro-geography.

In FIG. **X4**, micro-geography is similarly analyzed with molecular focusing depending on the pH of the substances in a substrate with and induced pH gradient, with molecules of low pH migrating toward the positive pole and molecules of high pH migrating toward the negative pole.

In FIG. **X5**, the moleculation apparatus is employed as a molecular computer for a complex reaction where A and B migrate on a convergent path producing C in a stable pH orbit. D migrates in an outward path reaches C to interact and produce the detected product E.

In FIG. **X6**, the moleculation apparatus is used to assist in detecting molecular memory vs. the central dogma and compares the conventional pathway of DNA (A) to RNA (B) to Proteins (C) with experimental pathways of Conformed molecule (X) to RNA intermediate (Y) to DNA (Z) that will confirm the inverse pathway hypothesis.

In FIG. **X7**, the moleculation apparatus is run at different or variable temperatures, for example to determine if a biological process varies in a warm blooded animal vs. a cold blooded animal.

In FIG. **X8**, the moleculation apparatus is used to detect the just noticeable difference phenomena. Reagents on a separate but merging path provide an opportunity to detect when their interaction is just noticeable, providing a means of capturing interactions as fuzzy and accurate processes.

In FIG. **X9**, the moleculation apparatus is used to observe staged biological processes, such as the conversion of proinsulin to insulin and biproducts, where Proinsulin (A) is on a convergent path with Trypsin (B) and reacts to produce Insulin (C) and (D) a C-reactive peptide.

In FIG. **X10**, the moleculation apparatus is used to mimic a biological cell with the micro-geography of the center being DNA representing the nucleus and a highly acidic environment.

In FIG. **X11**, the moleculation apparatus is used in just noticeable chemistry where A in the presence of B permits visualization of biochemical reaction in an environment analogous to in vivo environment.

In FIG. **X12**, the moleculation apparatus is used as a variable temperature device to understand "cold blooded" chemistry by comparative analysis with temperature as the variant.

It is to be understood that the foregoing exemplars are presented to demonstrate the different avenues that can be pursued when using the moleculation apparatus, and are not presented to limit the scope of this invention.

What is claimed is:

1. A moleculation device comprising:

electrophoretic apparatus having a substrate medium support structure with a stationary annular substrate medium support platform that is constructed to support an annular thin layer substrate medium;

an electrochargeable circular pole located substantially at the center of the substrate medium support platform; and,

an electrochargeable circular pole located substantially at the perimeter of the substrate medium support platform concentric with the center circular pole wherein the substrate medium support structure is constructed to receive selected test molecules in the substrate medium that are restricted by the construction of the support platform to migrate in a radial planar manner between the poles when oppositely charged and wherein the poles are selectively charged to induce the selected test molecules in the substrate medium to migrate toward the electrochargeable circular pole located substantially at the center of the substrate medium support platform.

2. The moleculation device of claim 1 wherein the substrate medium support structure includes a base and the substrate medium support platform includes a flat stage on which the annular substrate medium is supported.

3. The moleculation device of claim 2 further comprising a containment structure on the base arranged around the substrate medium support platform, wherein the substrate medium support platform includes an enclosed support wall on the base that elevates the flat stage above the base.

4. The moleculation device of claim 3 wherein the flat stage has a top surface and the containment structure is constructed to receive a liquid at least to a level that covers the top surface of the stage.

5. The moleculation device of claim 3 wherein the apparatus includes a thermal control system that controls the temperature of a substrate medium when supported on the flat stage of the substrate medium support platform.

6. The moleculation device of claim 1 wherein the annular substrate medium support platform of the substrate medium support structure has an annular substrate medium on the support platform that suspends molecules in the substrate medium for migration when the poles are oppositely charged.

7. The moleculation device of claim 6 wherein the substrate medium includes at least two interactive groups of molecules suspended in the substrate medium at separate locations when the poles are initially charged.

8. The moleculation device of claim 7 wherein the electrophoretic apparatus has a containment structure that is constructed to receive a liquid to a level that covers the substrate medium.

9. A moleculation device comprising:

an isoelectric focusing apparatus including a substantially flat migration field over which selected molecules having migration characteristics are induced to migrate;

a stationary migration medium on the migration field in which molecules are suspended for migration; and,

focusing means for establishing a convergent pH-gradient on the migration field wherein the focusing means includes an electric field generating apparatus having electrochargeable poles that are differently configured and are spaced apart on the flat migration field and selectively charged with an opposite polarity that induces separated molecule groups of different molecules to migrate in the migration medium in a substantially planar, nonparallel manner according to their migration characteristics to a location where the groups mix for molecular interaction.

10. The moleculation device of claim 9 wherein the migration field has a perimeter structure that forms a convergent migration field with a convergent migration medium.

11. The moleculation device of claim 9 wherein the migration field has ends wherein the spaced charged poles include a long pole at one end having a first charge and a short pole at the opposite end having a second opposite charge wherein a narrowing field of influence is generated when the poles are charged and separated groups of molecules in the migration medium on the migration field at the end proximate the long pole are induced to migrate according to their migration characteristics and mix during migration toward the short pole.

12. A moleculation device comprising:

an isoelectric focusing apparatus constructed with a stationary migration field that supports stationary molecule substrate mediums in a thin layer;

a molecule substrate medium that is adapted to suspend different groups of molecules having specific migration characteristics in the molecule substrate medium at different locations on the migration field for confluent mergers and collisional melding of the molecules in the groups; and,

a molecule migration inducement mechanism that has an electric field generating apparatus with spaced electrochargeable poles that are differently configured and oppositely charged wherein the migration mechanism operates with the migration field and generates an electric field that induces selected molecules in the substrate medium to migrate in accordance with their migration characteristics on planar nonparallel, convergent migration paths.

13. The moleculation device of claim 12 wherein the molecule migration field has a convergent structure limiting migration of molecules toward their isoelectric points.

14. The moleculation device of claim 13 wherein the molecule substrate medium has a pH gradient across the substrate medium on the convergent migration field.

15. The moleculation device of claim 13 wherein the molecule migration inducement mechanism comprises displaced poles on the convergent migration field that are differently sized to generate an asymmetric electric field.

16. The moleculation device of claim 13 wherein the convergent migration field is annular with a perimeter having an outer circular pole substantially around the perimeter and with a circular inner pole wherein the outer pole is substantially concentric to the inner pole.

17. A moleculation device comprising:

an isoelectric focusing apparatus constructed with a stationary convergent migration field that supports thin-layer molecule substrate mediums;

a thin-layer molecule substrate medium that is adapted to suspend different groups of molecules having select migration characteristics in the molecule substrate medium at different locations on the convergent migration field for confluent mergers and collisional melding of the molecules in the groups; and,

a molecule migration inducement mechanism that operates with the convergent migration field and induces molecules in the substrate medium to migrate on convergent planar migration paths, wherein the molecule migration inducement mechanism generates an electric field and comprises displaced poles on the convergent migration field that are oppositely charged, and wherein the convergent migration field is annular with a perimeter having an outer circular pole substantially around the perim-

eter and with a circular inner pole wherein the outer pole is substantially concentric to the inner pole and wherein the polarity of the poles is selected according to the select migration characteristics of the molecules in the groups of molecules to cause the molecules to migrate away from the outer perimeter pole toward the inner pole.

**18**. A moleculation device comprising:

an electrophoretic apparatus including a flat convergent migration field over which molecules are induced to migrate;

a stationary thin-layer migration medium on the migration field in which molecules are suspended for migration; and,

an electric field generating apparatus having spaced electrochargeable poles that are differently configured and wherein a convergent electrical field is generated coincident with the flat convergent field, wherein the polarity of the spaced poles is selected to induce separated molecule groups of different molecules to migrate in the migration medium in a planar nonparallel manner to a location where the groups mix for molecular interaction.

**19**. The moleculation device of claim **18** wherein the migration field has a perimeter structure that forms a convergent migration field with a convergent migration medium.

**20**. The moleculation device of claim **18** wherein the migration field has ends wherein the spaced charged poles include a long pole at one end having a first charge and a short pole at the opposite end having a second opposite charge, wherein a narrowing field of influence is generated when the poles are charged and separated groups of molecules in the migration medium on the migration field at the end proximate the long pole are induced to migrate and mix during migration toward the short pole.

**21**. A moleculation device comprising:

an electrophoretic apparatus constructed with a flat convergent migration field that supports molecule substrate mediums;

a stationary thin-layer molecule substrate medium that is adapted to suspend different groups of molecules having select migration characteristics in the molecule substrate medium at different locations on the migration field for confluent mergers and collisional melding of the molecules in the groups; and,

a molecule migration inducement mechanism that has an electric field generating apparatus with spaced electrochargeable poles that are differently configured and oppositely charged wherein the migration mechanism operates with the migration field and generates a convergent electric field that, when the electrochargeable polarity of the poles is selected according to the migration characteristics, the electric field induces molecules in the substrate medium to migrate on planar nonparallel, convergent migration paths.

**22**. The moleculation device of claim **21** wherein the molecule migration field has a convergent structure, limiting migration of molecules in the substrate medium.

**23**. The moleculation device of claim **22** wherein the molecule migration inducement mechanism comprises displaced poles on the convergent migration field that are differently sized to generate an asymmetric electric field.

**24**. The moleculation device of claim **22** wherein the convergent migration field is annular with a perimeter having an outer circular pole substantially around the perimeter and with a circular inner pole wherein the outer pole is substantially concentric to the inner pole.

* * * * *

## *A cancer 'brain-mind'*

| | |
|---|---|
| Restlessness | chemotherapy, radiation therapy and autovirulence effects |
| Forgetfulness | chemotherapy, radiation therapy and autovirulence effects |
| Impaired concentration | chemotherapy, radiation therapy and autovirulence effects |
| Memory lapses | chemotherapy, radiation therapy and autovirulence effects |
| Mistakes | seen in autovirulence and disorders in common sense |
| Misunderstandings | seen in autovirulence and disorders in common sense |
| Body language issues | chemotherapy, radiation therapy and autovirulence effects |

[NB: Body language issues refer to cultural interpretations of body language / image and health / illness conditions (e.g., interpretations of body and illness according to western and allopathic medicine, traditional Asian medicine, Ayurvedic medicine, shamanism et al.).]

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**Autism Prevalence Rates Around the World (2000-2008)**

| Continent/Region | Country | Approximate Prevalence Rate |
|---|---|---|
| North America | Canada | 65/10,000=1/154 |
| | United States | 66/10,000=1/152 |
| Caribbean | Haiti, Amer. and Brit. W. Indies, Martinique et al. | Insufficient data |
| Central America | Mexico, Guatemala, Costa Rica et al. | 20/10,000=1/500 |
| South America | Brazil, Venezuela, Chile, Peru et al. | 20/10,000=1/500 |
| Northern Europe | Finland | 12/10,000=1/833 |
| | Sweden (includes large immigrant population) | 53/10,000=1/86 |
| | Denmark | 12/10,000=1/833 |
| | Iceland | 13/10,000=1/769 |
| | UK and Ireland | 116/10,000=1/86 |
| Western Europe | Belgium, Luxemburg and The Netherlands | 20/10,000=1/500 |
| | Germany | 20/10,000=1/500 |
| | France | 20/10,000=1/500 |
| | Spain and Portugal | |
| | Principalities | |
| | Austria and Switzerland | |
| Southern Europe | Italy | 20/10,000=1/500 |
| | Greece, Crete, Malta et al. | 20/10,000=1/500 |
| Eastern Europe | Russia, Poland, Hungary, Czech and Slovak Republics et al. | Insufficient data |
| Southeastern Europe | Albania, Bulgaria, Montenegro, Serbia, Croatia, Romania, et al. | |
| Middle East | Syria, Lebanon, Israel, Saudi Arabia, Iran, Iraq, Qatar et al. | 10/10,000=1/100 |
| North Africa | Egypt, Libya, Morocco, Algeria et al. | Insufficient data |
| Mid-Equatorial Africa | Nigeria, | Insufficient data |
| Southern Africa | Angola, Botswana, South Africa, Zimbabwe, Zambia, Swaziland | |
| South-Central Asia | India, Bangladesh, Pakistan | Insufficient data |
| Eastern Asia | Japan | 89/10,000=1/116 |
| | China | Insufficient data |
| | Korea | Insufficient data |
| South-East Asia | Taiwan, Singapore, Thailand | Insufficient data |
| Southwestern Asia | Turkey | |
| Oceania | Australia | 39/10,000=1/256 |
| | New Zealand | 20/10,000=1/500 |
| | Papua New Guinea | 20/10,000=1/500 |

## *Encapsulation of Findings*

Succinctly, this report includes a cornucopia of findings:

1. It no longer is useful to conceive of cells and viruses as sacrosanct entities. By way of an analogy, just as atomic physicists found that by bombarding nuclei in a bubble chamber could produce elementary subatomic particles (e.g., quarks), cellular and viral substituents and secondary particles may play prominent and unique roles as transmissible, infectious, and pathogenic (though not necessarily replicatable) sources of cascading epigenetic and epigenomic consequences. The analogy ends there. This report underscores the extreme importance in distinguishing those autotoxic and autovirulent secondary particles, their aberrant *a priori* and *a posteriori* consequences, and expanded notions of epigenetics and epigenomics of diseases.
2. Stress-activated Epstein-Barr virus (EBV) *secondary* small RNA particles (i.e., autovirions) are transmissible, infectious and pathogenic (Smith, 1983; Smith, 1984; Smith, 2003a; Smith, 2009c). The transmissibility, infectiousness and pathogenicity of other small RNAs and microRNA now must be considered in microbiology, genetics, genomics, microbiology, and in other disciplines (cf. Wang et al., 2009). One also must consider and anticipate a broad array of pathogenic consequences attributable to those autovirulent particles. Most investigators overlook the potential transmissibility and infectiousness of intracellular products. This phenomenon was first described at a philosophy of science conference (Smith, 1983).
3. One can *infer* that pathogenic, “beneath-the-radar,” “hit-and-run” autovirions interfere with the genetic code by contributing to the production molecules derived from aberrant translation or transcription. The earliest instance of autovirulence was *inferred* and reported in 1983. Once prodded, a Japanese research team reluctantly revealed that increasing EBV infectious titers in cultured cells were associated with increasing titers of α–interferon and acid-labile α–interferon. This teaches that experimental and laboratory scientists may not fully appreciate the importance of logic, methodology and philosophy of science in contrast to brute force experimentation. It also teaches that scholarship in science requires “reading between the lines.”
4. The putative epigenetic mechanism is far more expansive than epigenetics typically reported by geneticists. Geneticists often limit discussions of epigenetics to methylation and imprinting. Their focus often is limited (e.g., histones). Our expanded notion of epigenetics generalizes the both Prusiner prion hypothesis and the Bishop-Varmus oncogene hypothesis. In the former case, the important issue is not proteinaceous infectious particles (i.e., prions) lacking nucleic acids. The general issue is that substituents or secondary particles are transmissible, infectious, and pathogenic – producing epigenetic consequences. Regarding the oncogene hypothesis, the more general issue goes beyond cancers and/or virus and retrovirus contributions. The general concern is about all aberrant products and aberrant functions. A recent report by Kelly et al. (2009) underscores the point beautifully. The investigators overlook possibilities that BHRF1 and the EBV bcl2 homologues in Burkitt’s lymphoma may be aberrant translation products associated with EBER-1 and/or EBER-2. Other reports also implicate potential

aberrant translation products associated with EBV (Dickerson et al., 2009) and gamma herpesviruses (Sathish, Zhu and Yuan, 2009). Perhaps most important, the putative epigenetic mechanism has profound implications for evolution insofar as the underlying mechanism could represent a significant *generator* of diversity, with selection factors then contributing to actual diversity. These findings teach the importance and limitations of *definitions* (cf. Ennis, 1974). A generalized notion of epigenetics ultimately must be instructive.

5. The putative mechanism can explain the etiologies of the *entire* autism spectrum, schizophrenia and selected other mental illnesses. Although it is uncommon to find a parsimonious explanation with one 'brush stroke', the underlying mechanism may have been missed because the perceived sanctity of the genetic code. 'Disciplined' scholars generally do not challenge 'taken-for-granted' (i.e., ethnomethodological) assumptions. Our findings teach that 'chance favors the prepared mind', and especially the "mind" receptive to LR and an expanded version of meta-analysis!
6. The claim that the putative mechanism can explain the etiologies of the *entire* autism spectrum is used advisedly. Our science teaches that Fragile X syndrome should not be considered in the autism spectrum. It is a trinucleotide repeat (TNR) disease and generally has a different etiologic basis. Our findings also teach that claims are misplaced regarding mercury being implicated in the etiology of autism. Methyl mercury, which binds to the EBV secondary small RNAs, could play a role in autism, but not ethyl mercury in post-natal vaccines. Lastly, controversies surrounding celiac disease and autism, and irritable and inflammatory bowel disorders and autism, may have merit, though only because of the vast array of stress-activated epigenetic aberrant products and/or their consequences contribute broadly to spectra of illnesses (cf. Vazirian, 2007; Babb and Stinnett, 2007). The important "take-home" message is that any symptoms associated with autovirulent actions may be associated with the autism spectrum.
7. Our findings teach that scientists (especially geneticists and "genomicists") should develop tools to screen for aberrant gene products (i.e., "noises" comprising aberrant protein sequences and conformations) and aberrant gene functions, in addition to screening for defective genes (i.e., "signals" indicating genetic diversity).
8. The putative mechanism has profound implications for evolution – and especially the evolution of hemoglobinopathies, selected *de novo* mutations, novel *in utero* (i.e., congenital) evolutionary processes never envisioned by Darwinists, and various idiopathic illnesses. As noted, transmissible and infectious autovirions may have contributed to the non-constant generation of diversity – *especially in an Equatorial region where EBV is hyper-endemic*. As we celebrate Darwin's 200$^{th}$ (February 12$^{th}$, 1809) birthday, my findings should remind readers that evolution remains an important, active and vibrant topic.
9. In regard to autism, the model posits that (glucocorticoid-mediated) stress-activated EBV leads to the release of autovirions in the pregnant female (i.e., *in utero*). Titers of autovirions (and titers of their aberrant translation products) in the unborn fetus(es) determine the entire autism spectrum. This thesis fundamentally shifts the paradigm about the etiology of autism from some post-natal factor to the

pregnant female, and underscores the importance of the medical management of stress during pregnancy. With the financial meltdown contributing to wholesale stresses (associated with losses in jobs, foreclosures, etc.), this finding and logistic reasoning point to the importance of anticipatory sciences – including the potential for anticipating chaos (Smith, 2009a; Smith, 2009b; Smith, 2009c)! This is the basis of the GPS metaphor.

10. The theory rejects the MMR vaccine (thiomersal) hypothesis as a cause of autism. Instead, the theory suggests that maternal exposure to methyl (not ethyl) mercury may contribute to pathogenicity insofar as methyl mercury can bind to autovirions. This finding also teaches the importance in digging deeply into issues of causality. It further teaches that pathology as a discipline must give way to more sophisticated pathogen analyses. By way of an analogy, one often hires a plumber to unplug a drain, though occasionally without exploring reasons underlying the upstream causes of the blockages. In the present context, pathogen analysis would be akin to 'purifying' and understanding aberrant molecular *functions* (in contrast to aberrant molecular *structures*).
11. Findings in this report pose fundamental ethnomethodological and logical challenges. For example, the transmissibility of autovirions *in utero* can mimic findings in classic studies of monozygotic and dizygotic twins. Autovirulence also can give rise to aneuploidies (especially mosaic aneuploidies), *de novo* mutations and other idiopathic findings. My passing comments about Sarah Palin's child ('Trig') having Down syndrome can be illustrative. Maternal stress in Sarah Palin's role as a neophyte Governor (and not age) could give rise to the Down syndrome aneuploidy – and especially when her daughter Bristol's concurrent infectious mononucleosis was being reported. This is a reminder of possible new ways for interpreting old data.
12. Just as Pauling, Itano, Singer and Wells (in 1949) reported using the then nascent electrophoresis technology for separating molecular *structures* to discover molecular / genetic diseases (e.g., sickle hemoglobin), my preliophic moleculator invention provides a novel molecular vectorial technology for elucidating normal and aberrant molecular *functions*. The latter technology may find utility in explaining which aberrant translation products give rise to aberrant cognitive, social, emotional and other findings in autism, schizophrenia and various mental disorders. As an example *and although yet unproven*, I cite possibilities that aberrant versions of neuroligin and/or neurexin may be critically important in autism and schizophrenia. I anticipate that, in the long-run, preliophics will prove to be central in making connections between aberrant molecules and higher-order neural-network concepts (e.g., aberrations in cognition, consciousness, beliefs, emotions, reality, awareness, attention, and social behavior as might be expected in autism or schizophrenia).
13. Not only are autovirions pathogenic, there is circumstantial evidence that their pathogenicity may have contributed to the deaths of Jesse Gelsinger and Jolee Mohr in ill-advised gene therapy experiments where adeno-associated vectors were used as vehicles for conveying genes. VAI and VAII small RNAs associated with adenoviruses now must be ruled out as etiologic factors in those deaths. More important, the biohazardous features of autovirions point to the importance of

highly secure laboratory environments (e.g., P3 facilities or higher). There also are potential national security implications. Our findings may represent the first concrete example in which one may *anticipate* biohazardous consequences.

14. Far-ranging implications include support for a long-standing (albeit little known) model that DNA is the repository of long-term memories (LTM) in brain, the immune system and selected other systems in organisms. The model could help explain the evolution and etiologies of trinucleotide repeat disorders (e.g., Huntington's disease, Fragile-X syndrome et al.). Regarding the evolution of LTM, the examples of platypus and echidna genomes are stark reminders that genome studies of platypus, echidna and other brains could be highly instructive.
15. Other long-range implications include a plethora of other known and 'to-be-discovered' (some of which may be anticipated) stress-activated illnesses, especially surrounding the extant global financial meltdown and the numerous stresses on individuals and families (Smith, 2009b). Indeed, a global stress surveillance program now should be considered by the World Health Organization, the US CDC, and other health agencies and ministries.
16. Philosophy of science implications go beyond Karl Popper's notion of verisimilitude insofar as logic and logistic reasoning (LR) challenge issues of experimentation and general experimental methods. For example, LR may provide guidance regarding which experiments are vacuous, those which may be contraindicated and those experiments that are essential. LR also may provide clarity regarding such diverse phenomena such as the Henle-Koch postulates and Ockham's razor. For example, it often is overlooked that the Henle-Koch postulates have no relevance regarding the issue of causality in HIV/AIDS because those postulates require that the offending pathogen be the sole cause of underlying disease. As for Ockham's razor, this report highlights the seminal failures of simple and disciplined approaches. The etiology of the autism spectrum disorders and schizophrenia would never be inferred under the William of Ockham scholasticism principle of simplification. Rather, parsimony must be the ultimate objective!

Ostensibly, this report is about the central role of epigenetics in evolution. Our notions of autotoxicity, autovirulence and context-specificity serve to unify a generalized prion hypothesis, a generalized oncogene hypothesis, and transmissible and infectious secondary particles that contribute to (i.e., generate) rapid, though stable, diversity – with selection factors determined by environmental influences.

## *Recommendations*

- Stress management
- Ethnographic cancer research
- Humility and best friends professionals
- Applications of logistic reasoning and preliophics in establishing cause … even retrospectively
- Anticipatory and logistic reasoning skills
- Deep translations of personal and professional experiences ,,, going beyond syntax and semantics Ie.g., translating between allopathic, traditional and other systems of beliefs and medicine)
- Reduction in internecine tendencies in cancer medicine
- Medical tourism, cross-border and treaty issues
- Increased need for *anticipatory* epidemiological and evolutionary analyses of stress-related events associated with war, trauma, catastrophies et al.

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