Past, Present, and Future of Orthomolecular Medicine

Jeffrey Bland, Ph.D., FACN, FACB
President, MetaProteomics

"The Past"

Sir Archibald Garrod
Roger Williams
Linus Pauling
Abram Hoffer


The Salience of Garrod's 'Molecular Groupings' and 'Inborn Factors in Disease'*

Summary: Garrod's important second book, Inborn Factors in Disease (1931), was about inherited predisposition to disease. Chemical and metabolic individuality, which are the modalities of predisposition, originated in 'molecular groupings' (proteins) in Garrod's view of life. Such 'groupings', as interlocus molecular hybrids, allelic complementation and expressions of modifier genes, can assume variant expression in heterozygotes. Here, it is shown that genetic variation in such 'molecular groupings' has clinical relevance, for example (1) in reproductive counseling for thalassaemia; (2) in clinical severity of 'monogenic' disease (e.g. familial hypercholesterolaemia and muscular dystrophy) when variation is not explained by allelic heterogeneity.

The associated chemical individuality in each case can be used to identify risk and thus as a mode of predictive medicine.

Sir Archibald E. Garrod, the founder of human biochemical genetics, attempted to interpret the whole organism's phenotype while dealing with its chemical parts.

"It has recently been pointed out by Bateson that the law of heredity discovered by Mendel offers a reasonable account of the inheritance of this condition... If it be a correct inference from the available facts that individuals of a species do not conform to an absolutely rigid standard of metabolism, but differ slightly in their chemistry as they do in their structure, it is no more surprising that they should occasionally exhibit conspicuous deviations from the specific type of metabolism that is considered normal."

--Sir Archibald Garrod, Lancet 1902; 1616-1620.

"Based essentially upon recent findings in genetics and biochemistry which have not been incorporated into medical thought, the concept of Genetotrophic Disease may lead to an understanding of many diseases whose etiology is at present obscure."

"A genetotrophic disease is one which occurs if a diet fails to provide a sufficient supply of one or more nutrients required at high levels because of the characteristic genetic pattern of the individual."


"A genetotrophic disease is one which occurs if a diet fails to provide a sufficient supply of one or more nutrients required at high levels because of the characteristic genetic pattern of the individual."


"The optimal concentrations of many nutrients for a person may differ greatly from the concentrations provided by the normal diet. Biochemical arguments support the idea that orthomolecular therapy may be preferred treatment for many health problems."


"Our interest in niacin began at the end of 1951 when exploring ideas with Dr. John Smythies. We thought that schizophrenia might be a disorder caused by a disorder of adrenalin metabolism in the body produced as substance with psychological effects like LSD...We decided to try niacin because it might compete for methyl groups and prevent noradrenalin being methylated to adrenalin."


"This article summarizes the evidence that certain vitamin deficiencies likely worsen the symptoms of schizophrenia, and the evidence that large doses of certain vitamins could improve the core metabolic abnormalities that predispose people to develop it."


As many as 1/3 of mutations in a gene result in the corresponding enzyme having an increased Michaelis constant or Km (decreased binding affinity) for a coenzyme resulting in a lower rate of reaction. About 50 human genetic diseases due to defective enzymes can be remediated or ameliorated by the administration of high doses of the vitamin component of the corresponding coenzyme, which at least partially restores enzymatic activity.

The Past, Present and Future of Orthomolecular Medicine
Jeffrey Bland, PhD

“The Present”

After an average of 4 years of supplementation, the combination of beta-carotene and vitamin A had no benefit and may have had an adverse effect on the incidence of lung cancer and on the risk of death from lung cancer, CVD, and any cause in smokers and workers exposed to asbestos. On the basis of these findings the RCT was stopped 21 months earlier than planned.


What did we learn from this trial? Smokers and heavy alcohol i.e. Charles Lieber and hepatic oxidation of carotenoids and retinoids.

Summary of RCT’s on Nutrient Supplements and CHD Risk

Supplementation with a small dose of vitamin E had only a marginal effect on the incidence of CHD in male smokers.


Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the EBCTCG (Epidemiological Collaboration on Thrombolytic Therapy).


Among the high risk individuals antioxidant supplements appeared to be safe. But, it did not produce any significant reductions in 5-year mortality from CVD, cancer, or other major outcomes.


The beneficial and adverse effects of tocopherol and carotene disappeared during the post intervention follow up. Smokers should avoid carotene.


The apparent beneficial results of high intake of antioxidant vitamins reported in observational studies have not been confirmed in large randomized trials. The discrepancy between different types of studies is probably explained by the fact that supplement use is a component in a cluster of healthy behaviors.


Maybe These Studies Employed the Wrong Approach to Evaluating the Effect of Supplementary Nutrients

We assume the same types of mechanism of action and low IC50 of nutrients as new-to-nature molecules But is this a correct assumption?
Concerns of trial design:
1. Not using the right type of supplement
2. Not using a high enough dose
3. Not using a complex antioxidant mixture
4. Not choosing the right population for study
5. Need to look at functional biomarkers
6. Not recognizing that antioxidants work as system in gene expression


Supplemental multivitamins, vitamin C, vitamin E, and folate were not associated with a decreased risk to lung cancer. Suplemental vitamin E was associated with a small increased risk. Patients should be counseled against using these supplements to prevent lung cancer.


In this large trial neither vitamin E nor vitamin C supplementation reduced the risk of major cardiovascular events. The data do not support the use of these supplements for the prevention of CVD in middle age or older men.


"High dose IV ascorbic acid was well tolerated but failed to demonstrate anticancer activity when administered to patients with previously treated malignancies. The promise of this approach may lie in combination with cytotoxic or other redox-active molecules."


Millimolar concentrations of extracellular vitamin C kill cancer cells but not normal cells”.

“The prescreening of patients with unique genetic sensitivities to specific vitamin-related functions for inclusion in intervention trials may likely determine those that are most likely to respond to specific orthomolecular interventions.”

–Alter Ther 2008; 14: 12-14.

“A ‘Pathway’ is only a strand from the physiological network

Life is composed of networks.
“Although new botanical drugs pose many challenges for both industry and the FDA, approval of the first botanical prescription drug shows they can be successfully met.”


The Most Significant Concepts of the Modern Era that Shape Medical Thought

- Gregor Mendel – Genetics
- Charles Darwin – Evolution

YOUR BOOK OF LIFE IN 23 CHAPTERS

Expressed Differently in Different Environments

What We Learned From the Human Genome Project

- The genome has far fewer genes than anticipated (20,000+)
- The variation of the genes is far greater than anticipated (3 million+ SNP’s)
- Our phenotype results from genes and environment that works through our epigenome
Pluripotent Stem Cells

- Dolly - The Sheep that Changed the World

Where are the cells in our body that can regenerate new organs? How do we enlist them as our ally in aging?

The Epigenome is the record of our personal history

- Chemical modifications to DNA and histone proteins modulate genome function
- The composition of the epigenome is a result of genetic determinants, lineage, and environment.

"Chemical modifications to DNA and histone proteins form a complex regulatory network that modulates chromatin structure and genome function. The epigenome refers to the complete description of these potentially heritable changes across the genome."

"Including epigenetics into epidemiological studies of human disease may help explain the relationship between the genome and the environment, and may provide clues for modifying these effects in disease prevention and therapy."

"We can only understand the physiology of folates if they are reviewed in a systems biology approach taking genetic uniqueness related to families of interdependent folate related genes into account such as MTHFR."

Hypomethylated
Methylated

EPIGENETIC
Versus
GENETIC

Gene Transcription
Chromatin reduces binding to basal factors and RNA pol II to very low levels.

Naked promoter binds RNA polymerase and basal factors.

Breadth factors → High levels of transcription

EPIGENETIC MODIFICATIONS
DNA Methylation
Histone Modifications

DNA METHYLATION
Methylated Promoter
Coding sequence
Transcription
Coding sequence
Folate, Epigenomic Instability and Colorectal Cancer Risk

"These data suggest that ESR1 methylation may play a role in subsequent adenoma recurrence."

Determining the causes and roles of genomic and epigenomic instability in colon tumor formation has the potential to yield more effective prevention strategies and therapeutics for patients with colorectal cancer.

"Low red blood cell folate levels enhance the effect of other risk factors for cervical dysplasia and in particular that of HPV infection."
--Butterworth, J Am Med Assoc 1977; 297: 528

Evidence Surrounding Methyl Nutrient Supplements and Hypermethylation

"Epidemiological studies suggest that a diet rich in fruits and vegetables protects against colorectal cancer. This effect may result from their high levels of folate."
--Intern J Oncology 2005; 26: 1469-54

"The concentration of folate intermediates in colorectal tumors are directly related to the presence of frequent DNA hypermethylation and inversely related to the presence of a common polymorphism in the MTHFR gene. Folate intermediates could serve as biochemical markers for the risk of developing the disease, as well as for the prediction of toxicity and efficacy of fluorouracil-based treatments."
--Clin Cancer Res 2003; 9: 5860-68

"Epidemiological studies suggest that a diet rich in fruits and vegetables protects against colorectal cancer. This effect may result from their high levels of folate."
--Intern J Oncology 2005; 26: 1469-54

"High dose folic acid supplementation is associated with a significant reduction in the occurrence of colonic adenomas suggesting that folic acid may be an effective chemopreventive agent for colorectal cancer."
The Past, Present and Future of Orthomolecular Medicine

Jeffrey Bland, PhD

Don’t Forget About Folate Cycle SNP’s like MTHFR

“...These data suggest that there could be two or more different molecular pathways in the development of gastric cancer, perhaps involving tumor suppression mechanisms and DNA repair.”

–World J Gastro 2003; 11: 3834-41

“...We conclude that low serum folate is a significant risk factor for osteoporosis with plasma Keys having a lesser effect. Both B12 and B6 by acting through may also have an effect on reduction of risk to osteoporosis.”

–Bone 2007; 40: 730-36

Epigenetic Methylation and Schizophrenia

Epigenetic regulation in human brain: focus on histone methylation

Epigenetic Methylation patterns may be heritable

“...These data are the first to contribute empirical support for the hypothesis that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life.”


Xenobiotic Influence on Epigenetics

- Michael Skinner….Environmental Epigenomics
- Randy Jirtle…Bis Phenol A and epigenetic marks
- M Szyf…Psychological stress and its influence on DNA methylation
- Heritable epigenetic marks…Autism? Methylation?
- Mercury/Xenobiotics?
- The future of Orthomolecular Medicine is connected to the nutritional genomic and epigenetic revolution

Recent Advances in Nutritional Sciences

“...Methylation is a reversible modification of DNA participating in epigenetic regulation of gene expression. It is now clear that aberrant DNA methylation is associated with aberrant DNA-methylation patterns. Based on evidence that global DNA hypomethylation coexists with hyperhomocysteinemia it is widely assumed that...”


“...shows that atherosclerosis is associated with concomitant hypermethylation and hypomethylation coexists with hyperhomocysteinemia it is widely assumed that aberrant DNA methylation patterns. Based on evidence that global DNA hypomethylation coexists with hyperhomocysteinemia it is widely assumed that...”

–Bone 2007; 40: 730-36

 Persistent epigenetic differences associated with prenatal exposure to famine in humans

“...These data are the first to contribute empirical support for the hypothesis that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life.”


The Future of Orthomolecular Medicine

- Environmental Epigenomics
- Bis Phenol A and epigenetic marks
- Psychological stress and its influence on DNA methylation
- Heritable epigenetic marks...Autism? Methylation? Mercury/Xenobiotics?
- The future of Orthomolecular Medicine is connected to the nutritional genomic and epigenetic revolution