

The Past, Present and Future of Orthomolecular Medicine

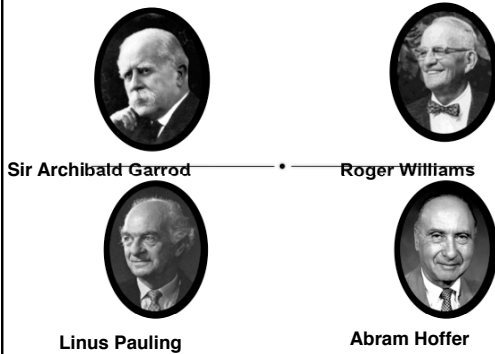
Jeffrey Bland, PhD

Past, Present, and Future of Orthomolecular Medicine

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

"The Past"

The Orthomolecular Revolution



The Incidence of Alkaptonuria: A Study in Chemical Individuality

By Archibald E. Garrod, M.A., M.D. Oxon

Physician to the Hospital for Sick Children, Great Ormond Street; Demonstrator of Chemical Pathology at St. Bartholomew's Hospital

All the more recent work on alkaptonuria has tended to show that the constant feature of this condition is the excretion of homogentisinic acid, to the presence of which substance the special properties of the urine are due.

excreting homogentisinic acid. After as much of the homogentisinic acid as possible had been allowed to separate out as the lead salt the small residue of alkapton acid was converted into the ethyl ester by a method

"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.

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*Originally published in *The Lancet*, pp. 1616-1620, 1902.

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■ J. Inher. Metab. Dis. 12 Suppl. 1 (1989) 9-24

■ 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 heterozygosity where the affected enzymes are normally homopolymeric; (3) 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.

ORIGINAL ARTICLES

THE CONCEPT OF GENETOTYPIC DISEASE

By Sir Archibald Garrod, M.A., M.D. Oxon

Physician to the Hospital for Sick Children, Great Ormond Street; Demonstrator of Chemical Pathology at St. Bartholomew's Hospital

It is a pleasure to me to be asked to contribute to this volume, which is devoted to the study of the incidence of alkaptonuria, a condition which is inherited in a recessive manner.

The study of the incidence of this disease has been a study in chemical individuality. It has been a study in the way in which the body is able to deal with the products of its metabolism. It has been a study in the way in which the body is able to deal with the products of its metabolism.

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NUTRITION REVIEWS
Vol. 9 SEPTEMBER, 1950 No. 9
CONCEPT OF GENETROTROPIC DISEASE

A genotrophic 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 concerned. (B. J. Williams, E. Rosenzweig, and L. J. Berry, *Lancet* 1, 897 (1950). This concept based upon recent results in genetics and biochemistry is new in medical thought and is believed to be the basis for many diseases, the manner of which is now obscure. In dietary patients are far from standardized.

"A genotrophic 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."

—Nutrition Reviews, 1950; 9: 257-59.

explains the difference between the dog and the rat in the efficiency of conversion of tryptophan into niacin (*Nutrition Reviews* 8, 897 (1950)).

The metabolic pattern of each person is different because of the characteristic that are inherited and distinctive. Urinary and blood analyses reveal these differences (H. C. Thompson and H. M. Kirby, *Arch. Biochem. Biophys.* 19, 407 (1950)).

Partial genetic blockade of the metabolic pathway is probably commoner in inborn errors of metabolism. Without an appropriate

supply of the particular nutrient (or nutrients) which an individual needs because of his own peculiar genetic pattern, nutritional (genotrophic) deficiency results.

Alcoholism was studied in its relation to individuality in metabolism. It was assumed in the beginning that the craving for alcohol has a physical and genetic basis similar to that of other special appetites that are under physiologic control. Experiments with rats and mice demonstrated, without serious doubt, that consumption of alcohol by individuals

able appetite for alcohol had been developed previously. Different strains, highly inbred and otherwise, gave results in line with the genetic hypothesis. Indeed a member of a highly inbred strain, with normal inbred pattern of a distinctive metabolic pattern based presumably on its own partial genetic blocks and on consequent suggested requirements for specific vitamins, exhibited a metabolic pattern which was different from that of the strain. The urge on the part of the individual to consume alcohol was conditioned by the existence of nutritional deficiencies. Although the physiologic nature of appetite itself is unknown, it is known that

SCIENCE
July 15, 1949, Vol. 58

The Inheritance of Sickle Cell Anemia¹
JAMES V. NEAL
Hereditary Clinic, Laboratory of Vertebrate Biology, University of Michigan, Ann Arbor

A DROP OF BLOOD is sufficient from each member of a family to determine the presence of the sickle cell trait. In the case of about 9 percent of the individuals composing the race a high proportion of the erythrocytes is "sick," as the phenomenon is commonly described, and is inherited by no pathological consequences in the majority of these individuals, and they are capable of having children, or the sickle cell trait, who are the victims of a severe, chronic, hereditary type of anemia known as sickle cell anemia. The gene portion has been variously estimated at between 1:1.4 (2) and 1:3.2 (1). The normal allele is known

was recognized as a clinical entity (3). On the basis of a study of one large family, Telford and Shull (12) concluded that the ability to make sickle hemoglobin is inherited as a dominant trait. At first some confusion between sickle cell and sickle cell trait, but it was soon strongly expressed in the present time. Several years ago, the author, in a review of the clinical features of the genetic carrier of sickle cell anemia (13), was led to suggest an alternative hypothesis—namely, that there existed in negro populations a gene which is heterogeneous conditionally to sickle cell anemia, and in heterozygous condition is sickle cell anemia. This hypothesis for a monogenic disease is supported, and in human beings, it is

and sickle, although occasionally, due to the disease, the two carriers, both parents may make. In estimating the exact proportion of carriers to be expected among the parents of individuals with sickle cell anemia according to the dominant hypothesis, the calculations must be made. To the best of the author's knowledge the question of the penetrance of the sickle cell gene has never been raised by those who have accepted the variable dominant hypothesis of inheritance. For purposes of estimating the number of carriers that would be expected to have a genetic basis not long after sickle cell anemia is observed, we shall assume that the gene is dominant. We shall further assume that the gene is fully penetrant and that the gene is fully penetrant and that the gene is fully penetrant. Finally, we shall assume on the basis of the clinical data that the frequency of those with sickle cell anemia is approximately 20 percent of normal, with the result that only a few individuals with this disease—on a

Orthomolecular Psychiatry
Varying the concentrations of substances normally present in the human body may control mental disease.

Linus Pauling

The methods principally used now for treating patients with mental disease are psychotropic (psychosomatic) and physical (psycho-somatic). The treatment of the brain is directed either to produce a chemical change in the brain or to produce a physical change in the brain.

"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."

—Linus Pauling, *Science* 1968; 160: 265-71.

Orthomolecular Psychiatry is a new concept in the treatment of mental disease. It is based on the principle that 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.

Orthomolecular Psychiatry is a new concept in the treatment of mental disease. It is based on the principle that 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."

—Lancet Feb 10, 1952; 316-18.

MASSIVE NIACIN TREATMENT IN SCHIZOPHRENIA
Review of a Nineteen-Year Study
J. H. CHAPMAN
J. H. CHAPMAN, M.D., F.R.C.P.
LATE MEDICAL DIRECTOR, ST. ALBANS HOSPITAL, ST. ALBANS, HERTS.

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Vitamin Therapy in Schizophrenia
Leonard John Hoffer, MD, PhD, Professor of Medicine
McGill University, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Quebec, Canada

Abstract: Schizophrenia is a devastating and poorly understood disease for which the only accepted therapy is long-term antipsychotic and anti-anxiety medication. 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."

—Int J Psychiatry Relat Sci, 2008; 45: 3-10.

Schizophrenia is a chronic disorder of brain function that affects perception, cognition, motivation and behavior. In predisposition, precipitating causes and pathophysiology are very poorly understood, but in at least chronic disease, likely to be strongly influenced by psychological factors. Lacking biological insight, psychiatrists diagnose schizophrenia purely from its clinical presentation, a practice that is known to be highly unsatisfactory but may be of some value in identifying patients whose symptoms are predominantly "positive" or "negative." For example, the first is a chronic disorder of brain function that affects perception, cognition, motivation and behavior. In predisposition, precipitating causes and pathophysiology are very poorly understood, but in at least chronic disease, likely to be strongly influenced by psychological factors. Lacking biological insight, psychiatrists diagnose schizophrenia purely from its clinical presentation, a practice that is known to be highly unsatisfactory but may be of some value in identifying patients whose symptoms are predominantly "positive" or "negative." For example,

High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K_m): relevance to genetic disease and polymorphisms¹⁻³
Bruce V. Bost, John Hoffer, David, and Erik A. Bost

Abstract: As many as one-third of mutations in a gene result in the corresponding enzyme having an increased Michaelis constant (K_m) or decreased binding affinity for its substrate. This is a common feature of many genetic diseases, resulting in a lower rate of reaction. About 50 human genetic diseases are due to defective enzymes, which are created or modified by the administration of high doses of the vitamin component of the corresponding enzyme, which at least partially restores enzymatic activity. Several single nucleotide polymorphisms, in which the variant amino acid reduces coenzyme binding, and thus enzymatic activity, are likely to be remedied by raising cellular concentrations of the cofactor through high-dose vitamin therapy. Some examples include the vitamin B₆-dependent enzyme, aspartate aminotransferase (EC 2.6.1.1), C-267 substitution at residue 677 (G77C>T) in *hcyh* (homocystidylase) (EC 2.3.1.3), and the vitamin B₁₂-dependent enzyme, methylmalonyl-CoA mutase (EC 5.4.3.1).

As many as 1/3 of mutations in a gene result in the corresponding enzyme having an increased Michaelis constant or K_m (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 enzyme, which at least partially restores enzymatic activity."

—Ames B. Am J Clin Nutr 2002; 75: 616-58.

the first is a chronic disorder of brain function that affects perception, cognition, motivation and behavior. In predisposition, precipitating causes and pathophysiology are very poorly understood, but in at least chronic disease, likely to be strongly influenced by psychological factors. Lacking biological insight, psychiatrists diagnose schizophrenia purely from its clinical presentation, a practice that is known to be highly unsatisfactory but may be of some value in identifying patients whose symptoms are predominantly "positive" or "negative." For example,

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Jeffrey Bland, PhD

"The Present"

THE NEW ENGLAND JOURNAL OF MEDICINE May 5, 1996

EFFECTS OF A COMBINATION OF BETA-CAROTENE AND VITAMIN A ON LUNG CANCER AND OTHER CAUSES OF DEATH IN A COHORT OF SMOKERS

Charles F. Lynch, M.D., Ph.D., University of Pittsburgh, Pittsburgh, Pa.; James R. Heath, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.; James F. Fraumeni, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.; James F. Fraumeni, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.; James F. Fraumeni, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.

Abstract. Background. Lung cancer and cardiovascular disease are the leading causes of death in smokers. Beta-carotene and vitamin A are antioxidants that may reduce the risk of these diseases. Objective. To determine the effects of a combination of beta-carotene and vitamin A 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. Design. A randomized controlled trial. Setting. The trial was conducted in the United States. Participants. 18,222 men aged 55 to 69 years who were smokers and workers exposed to asbestos. Interventions. The intervention group received a combination of beta-carotene and vitamin A, and the control group received a placebo. Measurements and Main Results. The trial was stopped 21 months earlier than planned because of a high incidence of death from lung cancer in the control group. The incidence of death from lung cancer was 1.5 times higher in the control group than in the intervention group. The incidence of death from CVD was 1.1 times higher in the control group than in the intervention group. The incidence of death from any cause was 1.1 times higher in the control group than in the intervention group. Conclusion. The combination of beta-carotene and vitamin A did not reduce the risk of death from lung cancer, CVD, or any cause in smokers and workers exposed to asbestos. On the basis of these findings the RCT was stopped 21 months earlier than planned.

—N Engl J Med 1996; 334: 1150-5.

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

Antioxidant vitamins in the prevention of cardiovascular disease: a systematic review

K. ASPLUND

From the Department of Medicine, University Hospital, Umeå and Swedish Council for Technology Assessment in Health Care, Stockholm, Sweden

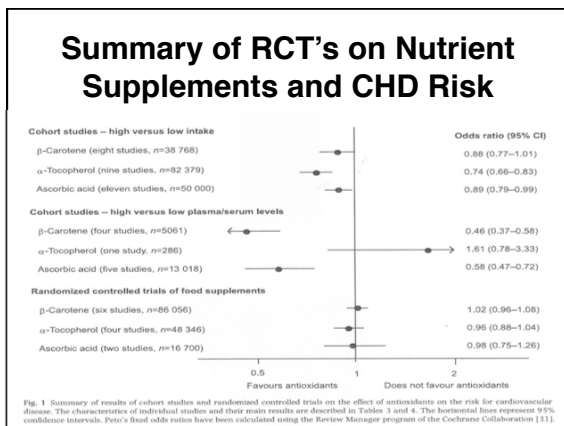
Abstract. Asplund K (Umeå and Stockholm, Sweden). Antioxidant vitamins in the prevention of cardiovascular disease: a systematic review. *Journal of Internal Medicine* 2002; 251: 372-92.

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.

—J Internal Med 2002; 251: 372-92.

Keywords: antioxidants, vitamins, oxidative stress, cardiovascular disease, carotenoids, tocopherol

Introduction. During the 1930s, studies in Australia showed that Seventh-day Adventists who had a diet rich in antioxidant acid and vegetable food showed blood pressure that control persons on a conventional diet (Ornsten). A low risk of cardiovascular death in subjects with a high intake of antioxidant acid was first reported in the 1950s (Lind et al.). Ecological studies performed in the United States later revealed a high mortality in myocardial infarction [2] and stroke [3] in men



Effect of Vitamin E and Beta Carotene on the Incidence of Primary Nonfatal Myocardial Infarction and Fatal Coronary Heart Disease

John A. Manson, M.D., Ph.D., Harvard Medical School, Boston, Mass.; Charles F. Lynch, M.D., Ph.D., University of Pittsburgh, Pittsburgh, Pa.; James F. Fraumeni, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.; James F. Fraumeni, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.; James F. Fraumeni, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.

Background. Oxidative low-density lipoprotein is a major risk factor for atherosclerosis. Antioxidant vitamins may reduce the risk of atherosclerosis by reducing the oxidation of low-density lipoprotein. Objective. To determine the effect of vitamin E and beta carotene on the incidence of primary nonfatal myocardial infarction and fatal coronary heart disease. Design. A randomized controlled trial. Setting. The trial was conducted in the United States. Participants. 18,222 men aged 55 to 69 years who were smokers and workers exposed to asbestos. Interventions. The intervention group received a combination of vitamin E and beta carotene, and the control group received a placebo. Measurements and Main Results. The trial was stopped 21 months earlier than planned because of a high incidence of death from lung cancer in the control group. The incidence of death from primary nonfatal myocardial infarction was 1.1 times higher in the control group than in the intervention group. The incidence of death from fatal coronary heart disease was 1.1 times higher in the control group than in the intervention group. Conclusion. The combination of vitamin E and beta carotene did not reduce the risk of death from primary nonfatal myocardial infarction or fatal coronary heart disease. On the basis of these findings the RCT was stopped 21 months earlier than planned.

—Arch Intern Med 1988; 238: 666-75.

"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 GISS-Prevenzione trial"

—Lancet 1999; 354: 447-59.

Incidence of Cancer and Mortality Following α-Tocopherol and β-Carotene Supplementation A Postintervention Follow-up

James F. Fraumeni, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.; Charles F. Lynch, M.D., Ph.D., University of Pittsburgh, Pittsburgh, Pa.; James R. Heath, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.; James F. Fraumeni, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.; James F. Fraumeni, M.D., M.Sc., University of Pittsburgh, Pittsburgh, Pa.

Abstract. Background. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a randomized controlled trial of the effects of α-tocopherol and β-carotene on the incidence of cancer and mortality in smokers. Objective. To determine the incidence of cancer and mortality following α-tocopherol and β-carotene supplementation. Design. A postintervention follow-up study. Setting. The trial was conducted in the United States. Participants. 18,222 men aged 55 to 69 years who were smokers and workers exposed to asbestos. Interventions. The intervention group received a combination of α-tocopherol and β-carotene, and the control group received a placebo. Measurements and Main Results. The trial was stopped 21 months earlier than planned because of a high incidence of death from lung cancer in the control group. The incidence of death from cancer was 1.1 times higher in the control group than in the intervention group. The incidence of death from mortality was 1.1 times higher in the control group than in the intervention group. Conclusion. The combination of α-tocopherol and β-carotene did not reduce the risk of death from cancer or mortality. On the basis of these findings the RCT was stopped 21 months earlier than planned.

—J Am Med Assoc 2003; 290: 476-85.

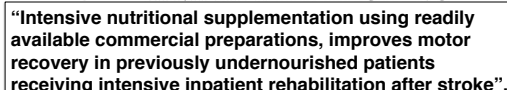
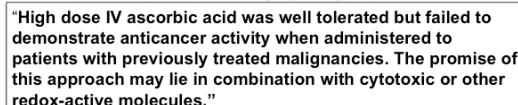
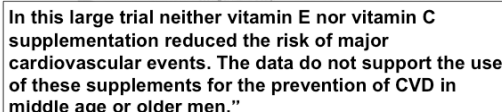
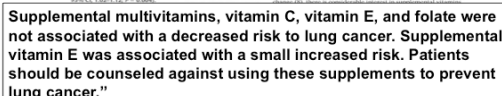
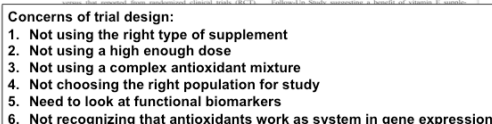
"Among the high risk individuals antioxidant supplements appeared to be safe. But, it did not produce any significant reductions in 5-year mortality from CVD, cancer, or other major outcomes."

—Lancet 2002; 360: 23-33.

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?

Jeffrey Bland, PhD



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"The Future"

Functional ● Medicine ● Update

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2008 Epigenetics Interviews

Randy Jirtle, PhD , Michael Skinner, PhD
Edward Calabrese, PhD , Michael Fenech, PhD

THE FUTURE OF NUTRITIONAL PHARMACOLOGY

Jeffrey Bland, PhD, FRCN, FRCR, is founder of the Institute for Functional Medicine, City Harbor, Washington. Learn more about Dr Bland at www.JeffreyBland.com. *Alter Ther Health* 2008; 14(12):12-14

"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.

Network pharmacology: the next paradigm in drug discovery

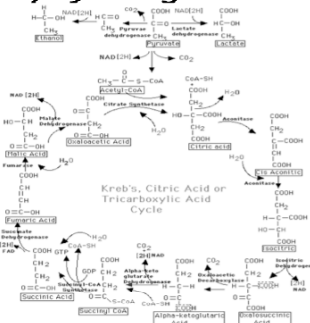
Andrew I. Hopkins

"The dominant paradigm in drug development is the concept of designing selective ligands to act on individual drug targets. However, many effective drugs act via modulation of multiple proteins rather than single targets. Advances in systems biology are revealing a phenotypic robustness and a network structure that strongly suggests that exquisitely selective compounds, compared with multi-target molecules may exhibit lower than desired clinical efficacy."

—Nature Chemical Biology 2008; 4: 682-88.

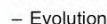
Life is composed of networks.

A "Pathway" is only a strand from the physiological network



Jeffrey Bland, PhD

Jeffrey Bland, PhD



- 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

The Past, Present and Future of Orthomolecular Medicine

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Pluripotential 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?

Genome Technology

'Omics for Stem Cells



What have we learned about stem cells and their epigenetics? Do the sperm and egg carry epigenetic messages? Are the messages all removed upon fertilization?

The Epigenome is the record of our personal history

The Mammalian Epigenome

Epigenetic modifications to DNA and histone proteins form a complex regulatory network that modulates the structure and function of the genome. The composition of the epigenome varies as a function of genetic determinants, lineage, and environment. With the sequencing of the human genome completed, investigators now seek to understand the epigenetic changes that determine how genetic information is used to build and maintain the body. The epigenome is a record of the developmental history of an individual, from the zygote to the adult, and it is a record of the environmental influences that shape the body. The epigenome is a record of the developmental history of an individual, from the zygote to the adult, and it is a record of the environmental influences that shape the body.

- Chemical modifications to DNA and histone proteins modulate genome function
- The composition of the epigenome is a result of genetic determinants, lineage, and environment.
- —Cell 2007; 128: 669.

Epigenetics at the Epicenter of Modern Medicine

Epigenetics, the study of non-DNA sequence-related heredity, is at the epicenter of modern medicine because it can help to explain the relationship between an individual's genetic background, the environment, aging, and disease. It can also help to explain the relationship between an individual's genetic background, the environment, aging, and disease. It can also help to explain the relationship between an individual's genetic background, the environment, aging, and disease. It can also help to explain the relationship between an individual's genetic background, the environment, aging, and disease.

"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."

—J Am Med Assoc 2008; 299: 1345-50.

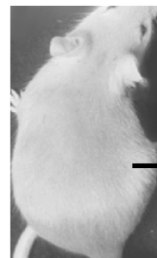
SYSTEMS BIOLOGY, FUNCTIONAL MEDICINE, AND FOLATES

Jeffrey Bland, PhD, MSc, is founder of the Institute for Functional Medicine, Gig Harbor, Washington. Learn more about Dr Bland at www.jeffreybland.com. (Altern Ther Health J 2008; 14:196-200)

"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."

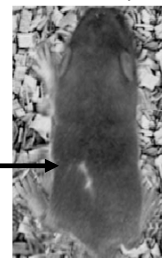
—Bland, Altern Ther 2008; 14: 196-200.

Hypomethylated



Traditional Agouti Mouse

Methylated

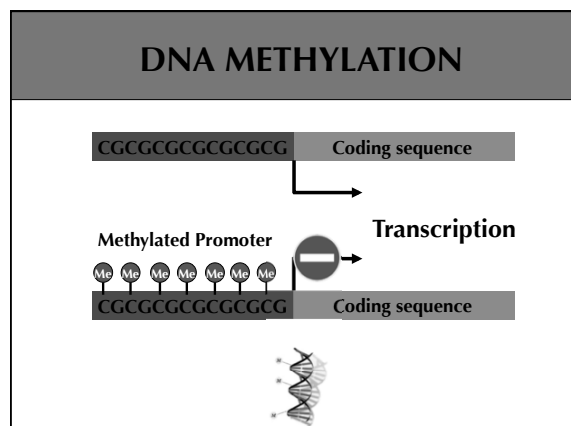
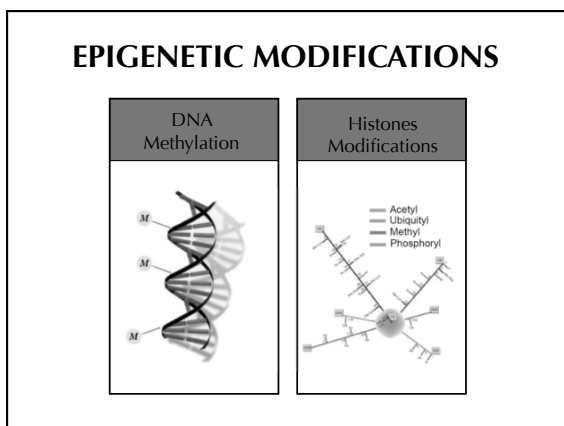
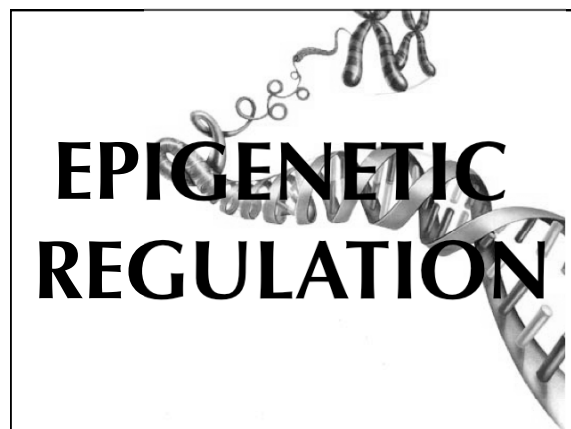
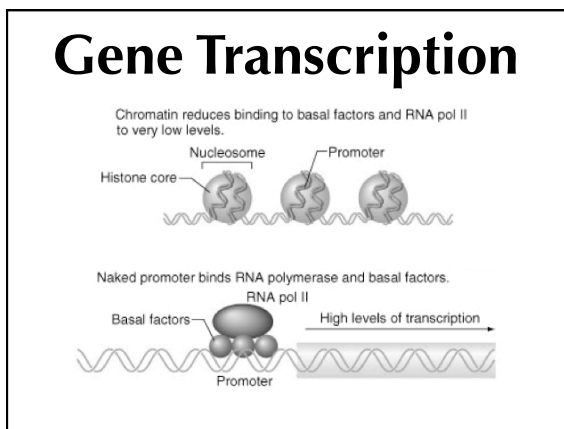
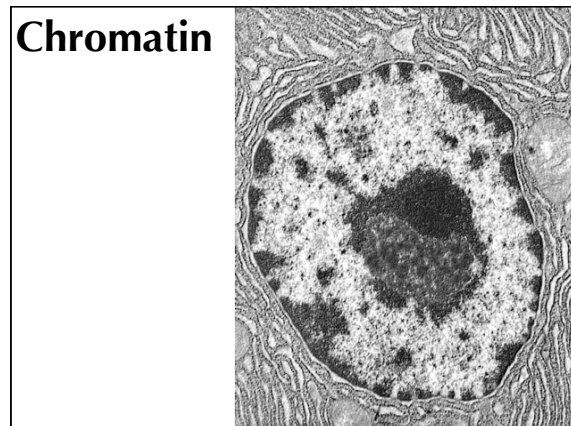
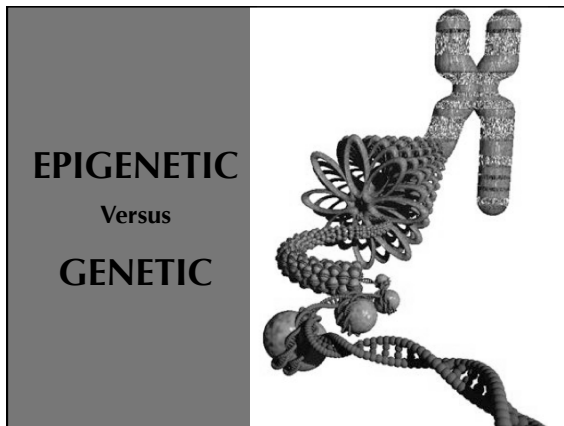


Epigenetic Agouti Mouse

Cooney et al. (2002) J Nutr. 132:2393S

The Past, Present and Future of Orthomolecular Medicine

Jeffrey Bland, PhD



Jeffrey Bland, PhD

[illegible][illegible]

<p>Thomas F. Chao, PhD Robert A. Bains, MD Robert S. Haines, MD Robert W. Haile, DrPH Robert W. Haile, PhD Robert S. Bresnahan, PhD Paul McCullough, DVM, PhD Robert W. Summers, MD Richard A. Anderson, PhD</p>	<p>Abstract Laboratory and epidemiological data suggest that folate <i>may</i> have an <i>adverse</i> effect on colorectal cancer risk. Objective: To assess the safety and efficacy of folate supplementation for prevention of colorectal cancer. Design, Setting, and Participants: A double-blind, placebo-controlled, 2-factor, randomized clinical trial involving 433 subjects and conducted between 6/1994 and October 1, 2004. Participants included 161 men and women with a recent history of colorectal adenoma or the presence of adenoma on colonoscopy. Intervention: Participants were randomly assigned to 1 g folic acid to maintain 10 nmol/L or 5 mg folic acid to maintain 20 nmol/L. Measurements and Main Results: The primary end point was the incidence of colorectal adenoma. The incidence of colorectal adenoma was 10.3% in the 1-g folic acid group and 10.5% in the 5-mg folic acid group. The incidence of colorectal adenoma was 10.3% in the 1-g folic acid group and 10.5% in the 5-mg folic acid group. The incidence of colorectal adenoma was 10.3% in the 1-g folic acid group and 10.5% in the 5-mg folic acid group. Conclusion: Folate supplementation did not increase the risk of colorectal adenoma.</p>
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increased tumor growth rate. Interestingly, less than half could up-regulate folate receptors, and antifolate drugs are effective in the majority of patients with advanced disease (16).

The overall chemopreventive effectiveness and potential for clinical application of folate supplementation in humans can be established only through randomized controlled trials. This issue contains two articles that present results of the first large chemoprevention trial investigating the effect of folate on the incidence of colorectal adenomas, the symbolic form of folate on the development of colon adenomas, established colorectal cancer precursors (see also p 235).

neous adenocarcinoma after the establishment of metachronous neoplastic foci in the colorectal mucosa may promote

Jeffrey Bland, PhD

• GASTRIC CANCER •

Effects of dietary intake and genetic factors on hypermethylation of the *hMLH1* gene promoter in gastric cancer

-World J Gastro 2005; 11: 3834-41.

M. Baines*, M.-B. Keadon, J. Usher, A. Davison, G. Higgins, W. Taylor,
C. West, W.D. Fraser, I.R. Farnsworth

—Bone 2007; 40" 730-36.

Nahid Yordanpanah,^{1,2,3} André G. Uitterlinden,^{1,2,3} M. Carola Zillikens,¹ Milla Bhamai,¹ Fernando Rivadeneira,^{1,2} Albert Hofman,² Robert de Jonge,² Jan Lindemans,⁴ Huibert A.P. Pols,^{2,4} and Joyce B. van Meurs²

Introduction: The MTHFR C677T polymorphism is associated with mildly elevated homocysteine (Hcy) levels in the presence of low folate and/or riboflavin status. A mildly elevated Hcy level was recently identified as a modifiable risk factor for osteoporotic fracture. We studied whether dietary intake of riboflavin and folate modifies the effects of the MTHFR C677T polymorphism on BMD and fracture risk.

–*J Bone Mineral Res* 2008; 23: 86-94.

Nutrition and Aberrant DNA Methylation Patterns in Atherosclerosis: More than Just Hyperhomocysteinemia?^{1,2}

ABSTRACT Methylation is a reversible modification of DNA participating in epigenetic regulation of gene expression. It is now clear that atherosclerosis is associated with

–J Nutr 2006; 135: 5-8.

RNA participating in epigenetic

Bastiaan T. Heijmans^{1,2}, Elmar W. Tobin^{1,2}, Anyeh D. Stein³, Hein Putter⁴, Gerard J. Blauw⁴, Ezra S. Susser^{2,5}, P. Eline Slagboom¹, and L. H. Lumey^{1,2}

is a heritable, environmentally sensitive trait that is determined by genetic factors in both adolescence and adulthood, indicating that the methylation mark is stable up to age 18. Thus, if affected by environmental conditions early in

developmental origins | DNA methylation | insulin-like growth factor II | nutrition | periconception.

–Proc Natl Acad Sci 2008; 105: 17046-49.

Biol Psychiatry. 2009 Feb 1;65(3):198-203.

Akbarian S. Huang HS.

Alterations in RNA levels are frequently reported in brain subjects diagnosed with autism, schizophrenia, depression,

Biol Psychiatry. 2009 Feb 1;65(3):198-203.

Akbarian S, Huang HS.

Alterations in RNA levels are frequently reported in brain subjects diagnosed with autism, schizophrenia,

■ Michael Skinner....Environmental Epigenomics

- Heritable epigenetic marks...Autism? Methylation? Mercury/Xenobiotics?

- The future of Orthomolecular Medicine is connected to the nutritional genomic and epigenetic revolution