# OFAS

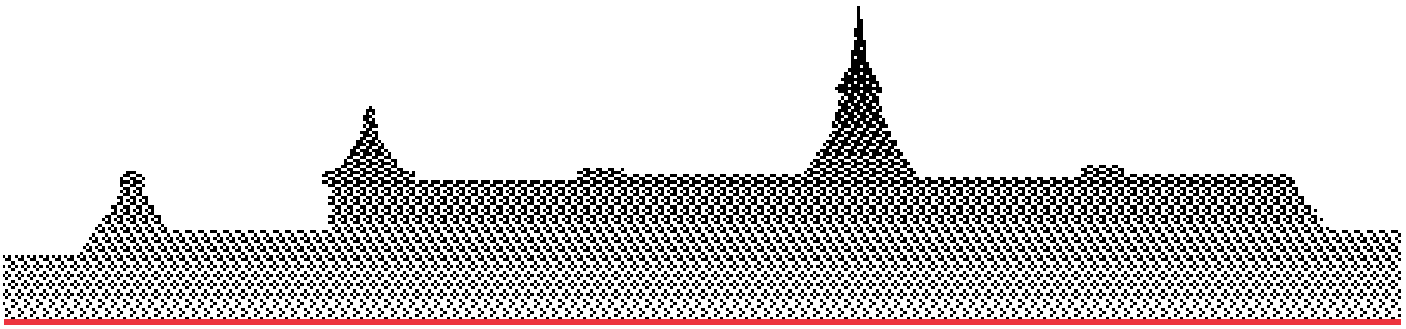
*Logo: Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.*

## 2006 Report

45

1961-2006

# Orentreich Foundation for the Advancement of Science, Inc.



Biomedical Research Station

Cold Spring-on-Hudson, NY

## Guide to Content of the 45th Anniversary Report



ST *Denotes studies using samples from the OFAS-KP Serum Treasury.*

MR *Denotes studies on the effects and mechanisms of a methionine-restricted diet.*

# Report of the Co-Directors

2006—the second year of our co-directorship—is the 45th anniversary of OFAS and its ongoing contributions to biomedicine.

The year was marked by two special events. OFAS became home to the World Health Organization Serum Reference Collection, which could no longer be maintained by the National Cancer Institute. (This resource is described on page 17.) Also this year, the Biomedical Research Station added an important new facility – the Archives Building. It provides much needed office space and a modernly equipped conference area that is utilized for weekly research meetings; it also houses our scientific periodicals collection, which pre-dates publicly available electronic sources.

ST *Denotes studies using samples from the OFAS-KP Serum Treasury.*

MR *Denotes studies on the effects and mechanisms of a methionine-restricted diet.*

The biomedical impact of OFAS has come predominately from two areas of investigation. The first is the search for advance clues to the development of diseases and their early diagnosis and prevention; this work utilizes the OFAS-KP Serum Treasury, which continues to be an exceptionally productive resource. The second is our pioneering research on a methionine-restricted diet, its effects on lifespan extension and disease prevention.

Lifespan extension is also the focus of our exploration into the effects of plasmapheresis on aging. As announced in last year's report, OFAS is engaged in evaluating plasmapheresis as an anti-aging procedure, revolutionary work originally begun by Alexis Carrel in the 1920-30s. (This project is described on page 13.)

In all regards, OFAS remains dedicated to biomedical research that focuses on developing interventions that prevent, halt, or reverse those disorders that decrease the quality or length of life.

We wish to express our gratitude to our generous supporters, dedicated staff, and superb collaborators, without whom OFAS's many accomplishments over the years would not have been possible.

Norman Orentreich, MD, FACP
Co-Director

David S Orentreich, MD
Co-Director

# Publications 2002-2006

**2002**

ST Shibata A, Parsonnet J, Longacre TA, Garcia MI, Puligandla B, Davis RE, Vogelman JH, Orentreich N, Habel LA
CagA status of *Helicobacter pylori* infection and p53 gene mutations in gastric adenocarcinoma.
*Carcinogenesis* 23(3):419-424, 2002.

ST Borofsky ND, Vogelman JH, Krajcik RA, Orentreich N
Utility of insulin-like growth factor-1 as a biomarker in epidemiological studies.
*Clinical Chemistry* 48(12):2248-2251, 2002.

ST Krajcik RA, Borofsky ND, Massardo S, Orentreich N
Insulin-like growth factor-I (IGF-I), IGF-binding proteins, and breast cancer.
*Cancer Epidemiology, Biomarkers and Prevention* 11(12):1566-73, 2002.

**2003**

MR Zimmerman JA, Malloy V, Krajcik R, Orentreich N
Nutritional control of aging. (Presented at the Neurobiology and Neuroendocrinology of Aging Conference, Bregenz, Austria, August 2002.)
*Experimental Gerontology* 38(1-2):47-52, 2003.

ST Shibata A, Parsonnet J, Longacre TA, Garcia MI, Puligandla B, Davis RE, Vogelman JH, Orentreich N, Habel LA
CagA status of *Helicobacter pylori* infection and p53 gene mutations in gastric adenocarcinoma. (letter, response)
*Carcinogenesis* 24(1):147, 2003.

ST de Martel C, Llosa AE, Farr SM, Friedman GD, Vogelman JH, Orentreich N, Parsonnet J
*Helicobacter pylori* infection and subsequent adenocarcinoma of the esophagus. (abstract)
*Gastroenterology* 125(2): 605-6, 2003.

ST Witherell HL, Smith KL, Friedman GD, Ley C, Thom DH, Orentreich N, Vogelman JH, Parsonnet J
C-reactive protein, *Helicobacter pylori,* chlamydia pneumoniae, cytomegalovirus and risk for myocardial infarction.
*Annals of Epidemiology* 13(3):170-177, 2003.

Krajcik RA, Vogelman JH, Malloy VL, Orentreich N
Transplants from balding and hairy androgenetic alopecia scalp regrow hair comparably well on immunodeficient mice.
*Journal of the American Academy of Dermatology* 48(5):752-59, 2003.

ST Krajcik RA, Massardo S, Orentreich N
No association between serum levels of tumor necrosis factor-α (TNF-α) or the soluble receptors sTNFRI and sTNFR2 and breast cancer risk.
*Cancer Epidemiology, Biomarkers and Prevention* 12(9):945-46, 2003.

**2004**

ST Munger KL, DeLorenze GN, Levin LI, Rubertone MV, Vogelman JH, Peck CA, Peeling RW, Orentreich N, Ascherio A
A prospective study of *Chlamydia pneumoniae* infection and risk of MS in two US cohorts.
*Neurology* 62:1799-1803, 2004.

MR Komninou D, Malloy V, Krajcik R, Rivensen A, Orentreich N, Richie JP.
Methionine restriction inhibits age-related spontaneous tumorigenesis in F344 rats. (abstract)
*Proceedings of the American Association for Cancer Research* 45: 3919, 2004.

MR Richie JP Jr, Komninou D, Leutzinger Y, Kleinman W, Orentreich N, Malloy V, Zimmerman JA
Tissue glutathione and cysteine levels in methionine-restricted rats.
*Nutrition* 20(9):800-5, 2004.

**2005**

ST de Martel C, Llosa AE, Farr AM, Friedman GD, Vogelman JH, Orentreich N, Corley DA, Parsonnet J
*Helicobacter pylori* infection and the risk of development of esophageal adenocarcinoma.
*Journal of Infectious Diseases* 191(5):761-7, 2005.

**2006**

ST DeLorenze GN, Munger KL, Lennette ET, Orentreich N, Vogelman JH, Ascherio A
Epstein-Barr virus and multiple sclerosis.
*Archives of Neurology* 63(6):839-44, 2006.

ST Iribarran C, Herrinton LJ, Darbinian JA, Tamarkin L, Malinowski D, Vogelman JH, Orentreich N, Baer D
Does the association between serum endostatin, an endogenous anti-angiogenic protein, and acute myocardial infarction differ by race?
*Vascular Medicine* 11(1):13-20, 2006.

MR Malloy VL, Krajcik RA, Bailey SJ, Hristopoulos G, Plummer JD, Orentreich N
Methionine restriction decreases visceral fat mass and preserves insulin action in aging male Fischer 344 rats independent of energy restriction.
*Aging Cell* 5(4):305-14, 2006.

## Archives Building

# Published Results

## *Infectious Agents and Cancer and Heart Disease*

### ***Helicobacter pylori* Infection Reduces the Risk of Subsequent Adenocarcinoma of the Esophagus**

Infection with *H. pylori* carries at least one benefit: a substantially lowered risk of esophageal cancer. Using samples from the OFAS-KP Serum Treasury, we looked for antibodies to *H. pylori* as proof of previous infection in 52 patients who developed adenocarcinoma of the esophagus. We also checked for antibodies in 551 controls who had other diseases, *i.e.,* lymphoma, colon cancer, gastric cancer, or heart disease. Only 38% of the persons who later developed cancer of the esophagus had antibodies whereas 62% was the average rate of infection for the control samples. We also found that infection with the particularly virulent CagA$^+$ strain of *H. pylori* did not modify the protective effect. That cigarette smoking was a strong independent risk factor for esophageal cancer was no surprise.

ST de Martel C, Llosa AE, Farr AM, Friedman GD, Vogelman JH, Orentreich N, Corley DA, Parsonnet J.
*Helicobacter pylori* infection and the risk of development of esophageal adenocarcinoma.
*Journal of Infectious Diseases* 191(5):761-7, 2005.

Collaborators: Departments of Health Research and Policy and Medicine, Stanford University School of Medicine; and Division of Research, Kaiser Permanente Medical Care Program

### **The Complex Role of Infection and Inflammation in Myocardial Infarction Risk**

Because heart disease is not always accounted for by traditional risk factors (*e.g.,* lipids, smoking, hypertension, etc.), it is important to discover other contributory factors, such as treatable infections. To this end we investigated the role of infectious agents in persons who had experienced a myocardial infarction (MI) and who had serum stored in the Serum Treasury. C-reactive protein (a marker of inflammation related to infection) was significantly associated with MI but only in those over age 51. The occurrence of MI was not correlated with infection by *Chlamydia pneumoniae* or cytomegalovirus; moreover, the levels of C-reactive protein did not reflect infection with these organisms.

ST Witherell HL, Smith KL, Friedman GD, Ley C, Thom DH, Orentreich N, Vogelman JH, Parsonnet J.
C-reactive protein, *Helicobacter pylori, Chlamydia pneumoniae,* cytomegalovirus and risk for myocardial infarction.
*Annals of Epidemiology* 13(3):170-7, 2003.

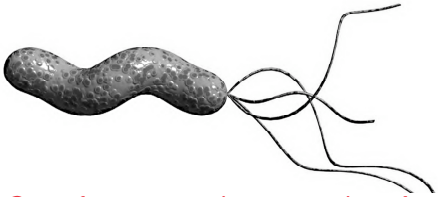
Collaborators: Departments of Health Research and Policy and Medicine, Stanford University School of Medicine; and Division of Research, Kaiser Permanente Medical Care Program

### **The Importance of the Strain of *Helicobacter pylori* in Stomach Cancer**

Stomach cancer is the second most prevalent cancer in the world, especially in Asia, Latin America, and some European countries. This cancer is strikingly associated with earlier infection by the bacterium *H. pylori,* of which the particular strain CagA$^+$ is more strongly associated with risk. Our study showed that tumors from persons previously infected with this virulent strain were more apt to show a mutation of the p53 tumor suppressor gene, a well-studied gene that is frequently mutated in various types of human cancer.

ST Shibata A, Parsonnet J, Longacre TA, Garcia MI, Puligandla B, Davis RE, Vogelman JH, Orentreich N, Habel LA.
CagA status of *Helicobacter pylori* infection and p53 gene mutations in gastric adenocarcinoma.
*Carcinogenesis* 23(3):419-24, 2002.

Collaborators: Departments of Health Research and Policy and Medicine, Stanford University School of Medicine; Department of Pathology and Division of Research, Kaiser Permanente Medical Care Program; and Metabolism Branch, National Cancer Institute



*One of some two dozen species of* Helicobacter *that reside in the intestinal tract of animals and human beings,* H. pylori *is between 2.5 and 5.0 microns long and lives beneath the mucus layer of the stomach.*
Courtesy of Luke Marshall, Helicobacter Foundation

## *Infectious Agents and Multiple Sclerosis*

### Antibodies to EBV, which Increases Risk of MS 10-fold, are Detectable 15-20 Years Before Diagnosis

In meta-analysis of the literature, individuals who had antibodies to Epstein-Barr virus (EBV) were at 10-fold risk of developing Multiple Sclerosis (MS). In further support of an association between EBV infection and subsequent MS, increasing anti-EBV antibodies were found as long as ten years before diagnosis of MS. Our study was the first MS-EBV investigation to use a prospective study design with a very long period of follow-up. Our research found that anti-EBV in MS patients occurred between 15 to 20 years before the onset of symptoms and persisted thereafter. A finer understanding of the mechanisms that connect EBV infection to MS will provide new ways to treat and prevent MS.

ST DeLorenze GN, Munger KL, Lennette ET, Orentreich N, Vogelman JH, Ascherio A.
Epstein-Barr virus and multiple sclerosis.
*Archives of Neurology* 63(6):839-44, 2006.

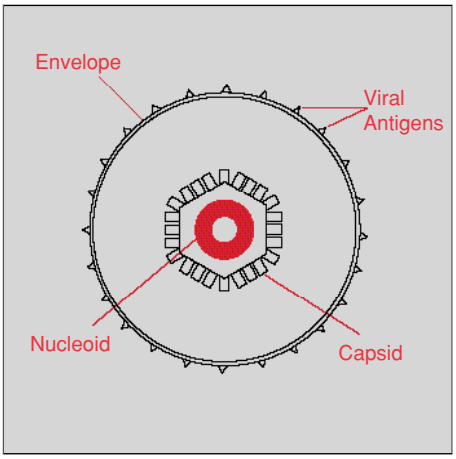
Collaborators: Division of Research, Kaiser Permanente Medical Care Program; Departments of Nutrition and Epidemiology, Harvard School of Public Health; and Virolab, Inc

### Infection with *Chlamydia pneumoniae* Does Not Cause, but May Influence the Development of, Multiple Sclerosis

Some people with Multiple Sclerosis (MS) have antibodies to the bacterium *Chlamydia pneumoniae;* others do not. To determine if previous infection with *C. pneumoniae* increases the risk of developing MS, our study looked for markers of infection in serum of persons who developed MS up to 20 years after donating serum, either to the OFAS-KP Serum Treasury or to the Department of Defense Serum Repository. The likelihood of developing MS after this infection was not increased, but the results allow for the possibility that infection somehow modifies the risk.

ST Munger KL, DeLorenze GN, Levin LI, Rubertone MV, Vogelman JH, Peck CA, Peeling RW, Orentreich N, Ascherio A.
A prospective study of *Chlamydia pneumoniae* infection and risk of MS in two US cohorts.
*Neurology* 62:1799-1803, 2004.

Collaborators: Departments of Nutrition and Epidemiology, Harvard School of Public Health; Division of Research, Kaiser Foundation Research Institute; Division of Preventive Medicine, Walter Reed Army Institute of Research; Army Medical Surveillance Activity, US Army Center for Health Promotion and Preventive Medicine; US Army Physical Disability Agency; National Laboratory for Sexually Transmitted Diseases, National Microbial Laboratory (Canada); and Department of Medicine, Brigham and Women's Hospital and Harvard Medical School




**Structure of the Epstein-Barr Virus**
The infectious virus particle consists of three components: a doughnut-shaped central core (Nucleoid) which contains the viral DNA in condensed form; a Capsid, which is made up of hollow, tubular protein subunits called capsomeres; and a protective Envelope incorporating Viral Antigens



## *Heart Disease and Endostatin*

### The Benefits of High Endostatin Levels are Race-dependent

Endostatin inhibits the formation and growth of blood vessels, a process called angiogenesis. Angiogenesis in plaques is often present in atherosclerotic vessels, and common factors could cause plaque disruption, the event that usually causes acute myocardial infarction (AMI). For all the medical complications of Down's Syndrome, it has two distinct pluses: 1) lower risk of cancer and 2) despite high triglycerides and lower HDL levels, there is virtually no atherosclerosis; both pluses are likely due to high levels of endostatin. Our study found that, all other risk factors being equal, a high level of circulating endostatin (in serum samples from healthy persons antedating AMI by even decades) is associated (in either sex) with decreased risk of AMI. Curiously, the finding was only for Asians and whites but not for blacks who, in fact, show the opposite association, a phenomenon that likely reflects ethnic differences in endostatin gene expression.

ST Iribarran C, Herrinton LJ, Darbinian JA, Tamarkin L, Malinowski D, Vogelman JH, Orentreich N, Baer D.
Does the association between serum endostatin, an endogenous anti-angiogenic protein, and acute myocardial infarction differ by race?
*Vascular Medicine* 11(1):13-20, 2006.

Collaborators: Division of Research, Kaiser Permanente Medical Care Program; CytImmune Sciences, Inc; and Department of Oncology, Kaiser Permanente Oakland Medical Center

# Published Results

## *Breast Cancer and Insulin-like Growth Factor*

**Breast Cancer Risk is Not Increased by TNF Receptor Levels**

Tumor Necrosis Factor-α (TNF-α) is critical in maintaining resistance to infection and malignancy, and its beneficial action can be blocked by soluble TNF receptors. Using the OFAS-KP Serum Treasury, we found that TNF receptor levels rise with age and with body mass index (BMI), but that neither abnormally high nor high-normal levels are associated with increased risk of breast cancer.

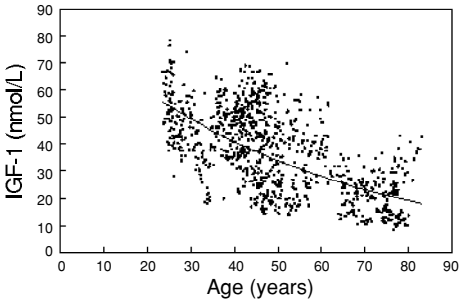
ST Krajcik RA, Massardo S, Orentreich N.
No association between serum levels of tumor necrosis factor-α (TNF-α) or the soluble receptors sTNFRI and sTNFR2 and breast cancer risk.
*Cancer Epidemiology, Biomarkers and Prevention* 12(9):945-6, 2003.

**Menopausal Status Affects Breast Cancer Risk Relative to Insulin-like Growth Factor-1**

Insulin-like Growth Factors (IGFs) and their binding proteins (IGFBPs 1, 2, and 3) play a role in the induction and progression of various cancers (*e.g.,* colon, prostate). Because estrogen both regulates and is influenced by the IGF family, we studied the relationship of breast cancer risk relative to IGF and its binding proteins in pre- and postmenopausal women. Risk was increased in premenopausal women who had elevated levels of IGF-1 and IGFBP-3. On the positive side, elevated levels of IGFBP-2 correlated with decreased risk of postmenopausal breast cancer.

ST Krajcik RA, Borofsky ND, Massardo S, Orentreich N.
Insulin-like growth factor-1 (IGF-1), IGF-binding proteins, and breast cancer.
*Cancer Epidemiology, Biomarkers and Prevention* 11(12):1566-73, 2002.

## *Insulin-like Growth Factor*




**Disease Risk Can be Assessed by a Single Measurement of Insulin-like Growth Factor-1 in Stored Serum**

Several common cancers (prostate, breast, colorectal, and lung) are associated with high serum levels of Insulin-like Growth Factor-1 (IGF-1), whereas low levels of this growth factor are associated with osteoporosis, impaired cognition, and heart disease. In anticipation of studies of these diseases, we evaluated the reliability of assays of IGF-1 in frozen serum samples from the OFAS-KP Serum Treasury. Our study used samples both fresh and stored up to 16 years from the same persons. We found that each participant's serum level of IGF-1 remained relatively constant and, confirming previous results, that IGF-1 levels were lower in persons over 45 and declined with age in the two individuals for whom there were long-stored samples. From this study we conclude that a single IGF-1 determination is reliable for use in estimating disease risk after adjusting for age.

ST Borofsky ND, Vogelman JH, Krajcik RA, Orentreich N.
Utility of insulin-like growth factor-1 as a biomarker in epidemiological studies.
*Clinical Chemistry* 48(12):2248-51, 2002.

## *Hair Regrowth*

**Balding Hairs Grow Long and Thick on Immunodeficient Mice**

Because immunodeficient mice do not reject foreign tissues, they accept transplants of human hairs that can then be studied. We transplanted both miniaturized and normal hair follicles from scalp affected by common balding. Our study found that miniaturized hair follicles can quickly regenerate once removed from the human scalp; in fact, they grew as well as or better than the transplanted normal, non-balding hair follicles as assessed by diameter and length achieved at 22 weeks.

Krajcik RA, Vogelman JH, Malloy VL, Orentreich N.
Transplants from balding and hairy androgenetic alopecia scalp regrow hair comparably well on immunodeficient mice.
*Journal of the American Academy of Dermatology* 48(5):752-9, 2003.

**Methionine Restriction (MR): Less Fat Accretion without Calorie Restriction (CR)**

To determine if CR is a coincidental but essential/inherent component of how MR achieves the same benefits as CR, we fed rats either MR or a normal diet of equal caloric content. The results definitively showed that CR is not an essential part of MR's ability to prevent accretion of visceral fat, maintain a youthful response to an oral glucose tolerance test, and keep serum lipids (especially triglycerides) from creeping up with age. Neither are the benefits the result of coincidental protein restriction; protein intake was, in fact, higher in the MR animals.

Malloy VL, Krajcik RA, Bailey SJ, Hristopoulos G, Plummer JD, Orentreich N.
Methionine restriction decreases visceral fat mass and preserves insulin action in aging male Fischer 344 rats independent of energy restriction.
*Aging Cell* 5(4):305-14, 2006.

**Restricting Dietary Methionine Quickly Benefits Glutathione Levels**

Glutathione is an important stabilizer of cell function, and decreased levels have been implicated in the aging process and in the development of numerous chronic diseases. We know that lifespan is significantly extended by a life-long diet that is either CR or MR. Unlike CR, a MR diet increases glutathione levels and prevents the usual decrease of glutathione that occurs with aging. Our study found that the beneficial changes in glutathione levels were evident within only one week of starting MR. Interestingly, the increase of glutathione was in the red blood cells, not in whole plasma (where, in fact, the levels went down). Further, although levels of glutathione in the liver were quickly and greatly reduced, they were beneficially conserved in most non-liver tissues.

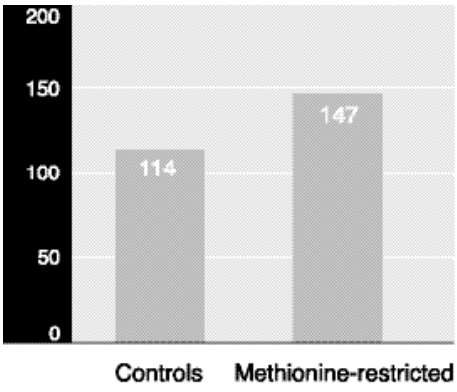
Richie JP Jr, Komninou D, Leutzinger Y, Kleinman W, Orentreich N, Malloy V, Zimmerman JA.
Tissue glutathione and cycteine levels in methionine-restricted rats.
*Nutrition* 20(9):800-5, 2004.

Collaborator: American Health Foundation Cancer Center

**Caloric Restriction vs Selective Amino Acid Restriction: Both Extend Lifespan, but…**

A 40% reduction in calories is a well-established means of extending lifespan in rodents and other species, but the deprived research subjects are irritable. We also know that restriction of a single amino acid, tryptophan, extends lifespan in rodents. Elimination of the amino acid cysteine in combination with minimal methionine intake produces 40% lifespan extension while maintaining normal or enhanced levels of the antioxidant glutathione, and it does so without any restriction of food intake. We evaluated MR in several strains of rats. Because this diet produced extended lifespan in strains that have differing pathologic profiles of aging, it can be concluded that MR genuinely alters the rate of aging in rats, probably by delaying its start.

Zimmerman JA, Malloy V, Krajcik R, Orentreich N.
Nutritional control of aging. (Presented at the Neurobiology and Neuroendocrinology of Aging Conference, Bregenz, Austria, August 2002.)
*Experimental Gerontology* 38(1-2):47-52, 2003.




**Median lifespan in weeks of Fischer 344 male rats**

# New Research Results

## Prostate Cancer, Race, and Insulin-like Growth Factors

*Risk of prostate cancer is about two times greater for blacks than whites. Our study found that higher levels of IGF-1 seem to confer modest protection for whites but not blacks. Lower levels of IGF-2 and IGFBP-3 among blacks contribute to their higher risk of this cancer.*

Blacks develop prostate cancer (PC) about two times more frequently than whites. Two possibilities: the black rate is normal and whites are protected by some factor(s), or the white rate is normal and black risk is increased by some factor(s). Studies of racially mixed populations report conflicting findings on risk of PC in association with the Insulin-like Growth Factor (IGF) family of proteins, but most of these studies did not analyze the results by race. Our study of 89 white and 94 black men (with carefully matched controls) was designed to elucidate the effects of the IGF family of proteins specifically by race. The lowest PC risk occurred in the highest quartile of IGF-I for both blacks and whites, whether lumped together or analyzed by race. PC risk decreased as IGF-II levels increased for blacks and whites when lumped together—but only for blacks when analyzed by race. However, the apparent protective effect of IGF-II was lost after adjustment for IGF Binding Protein-3. The various racial differences that our study uncovered show that the IGF family of proteins confound analyses of mixed race studies and account for the discrepant results found in previous studies. *Submitted for publication.*

ST Krajcik RK, Massardo S, Van Den Eeden SK, Quesenberry C, Orentreich N.
Prostate cancer risk associated with metabolic syndrome: A prospective study in black and white men.

Collaborator: Division of Research, Kaiser Permanente Medical Care Program

## Prostate Cancer and Metabolic Syndrome

*The classic symptoms of Metabolic Syndrome as a whole are a risk factor for prostate cancer.*

About 25% of the US population has Metabolic Syndrome, a set of physiologic and endocrine abnormalities arising from lifestyle (Western diet, sedentary behavior) and genetic predisposition. Its hallmark is insulin resistance in tissues. Overproduction of insulin compensates for the insulin resistance, but high levels of circulating insulin might increase the risk of prostate cancer (PC) by directly or indirectly stimulating the growth of prostate cells. We analyzed the Metabolic Syndrome risk factors and cholesterol, LDL-cholesterol, C-Reactive Protein, insulin, leptin, uric acid, and Prostate Specific Antigen (PSA). Metabolic Syndrome predicts PC risk with each added component increasing the risk by about 25%, but no one component of the Syndrome independently predicts the development of cancer or enhances the predictive ability of the Syndrome as a whole. There were no significant racial differences, but, confoundingly, high levels of leptin conferred protection to blacks and increased risk to whites. *Submitted for publication.*

ST Krajcik RK, Massardo S, Van Den Eeden SK, Quesenberry C, Orentreich N.
Racial differences in prostate cancer risk associated with insulin-like growth factors and their binding proteins: A prospective study in black and white men.

Collaborator: Division of Research, Kaiser Permanente Medical Care Program

## Food Contaminant

*Aflatoxin is a probable carcinogen that occurs naturally with poorly-stored grains. Although serum levels in US persons were low, they were surprisingly prevalent.*

The International Agency for Research on Cancer lists aflatoxin as a probable carcinogen, especially affecting the liver. Aflatoxin is a metabolic byproduct of certain species of *Aspergillus* fungus that naturally contaminate crops such as cereal grains, spices, groundnuts, and treenuts during cultivation, harvest, or storage. When storage quality is poor (warm/moist), 80-100% of the population will have serum levels that might be as high as 1000 pg/mg/albumin but more typically ~50 pg/mg. In serum collected in the 60s and 70s from citizens of the US, where storage quality is generally high, 20% had some detectable aflatoxin, but the mean level was only 5.9 pg/mg. That serum stored for 35+ years can be used to measure aflatoxin will enable investigators to look for associations between aflatoxin exposure and long-term health consequences. *Submitted for publication.*

ST Van Den Eeden SK, Wild CP, Vogelman JH, Orentreich N.
Aflatoxin-albumin adduct levels in stored serum from California.

Collaborators: Division of Research, Kaiser Permanente Medical Care Program; and The LIGHT Laboratories

## Infectious Agents and Pancreatic Cancer

The five-year survival rate for pancreatic cancer is only about 4% (the worst for any malignancy) making it the fourth leading cause of cancer death in the US. Infection with *H. pylori* is causally associated with gastric cancer and gastric lymphoma, and there is evidence that *H. pylori* might be associated with pancreatic cancer. Using serum stored decades before diagnosis of 104 cases (and controls), our study found that *H. pylori* infection is not a risk factor for pancreatic cancer. In light of our and others' findings, the relationship between this infection and pancreatic cancer is not a simple one, *i.e.,* it can have a protective, deleterious, or null among different subsets of subjects, characterized by some still unrevealed genetic, immunologic, or environmental factor. *Submitted for publication.*

*In various subsets of people,* H. pylori *infection can have a protective, deleterious, or null effect for pancreatic cancer.*

ST de Martel C, Llosa AE, Friedman GD, Vogelman JH, Orentreich N, Stolzenberg-Solomon RZ, Parsonnet J.
*H. pylori* infection and the development of pancreatic cancer.

Collaborators: Division of Research, Kaiser Permanente Medical Care Program; and The LIGHT Laboratories

## Infectious Agents and Esophageal Cancer

Recent studies have shown a significant negative association between *H. pylori* infection and esophageal cancer, but it is not clear why or how. One hypothesis is: infection → gastric atrophy → less acid production → reduced exposure of the esophagus to refluxed acid, the strongest risk factor. Strongly against this hypothesis are several facts: infection does not typically change gastric pH, and biomarkers of gastric atrophy do not correlate very well with risk of gastric or esophageal cancer. We asked if the appetite-stimulating peptide ghrelin was involved. Why? For several reasons: ghrelin levels are normally high before eating and low afterwards; ghrelin markedly increases gastric acid secretion; persons with *H. pylori*-induced chronic gastritis have impaired ghrelin secretion (less acid secretion); and eradication of the infection restores ghrelin and acid levels. Surprisingly, our findings were that high, not low, ghrelin levels appear protective against esophageal cancer, but the protection was only in overweight persons who normally (though inexplicably) have low levels of ghrelin compared to lean persons. Incidentally, obese persons have a much greater risk of gastric cancer, infected or not. *Submitted for publication.*

H. pylori *infection protects against this cancer, but the mechanism still eludes us after one more candidate component, ghrelin, has been eliminated.*

ST de Martel C, Haggerty TD, Corley DA, Vogelman JH, Orentreich N, Parsonnet J.
Serum ghrelin levels and risk of subsequent adenocarcinoma of the esophagus.

Collaborators: Departments of Health Research and Policy and Medicine, Stanford University School of Medicine; and Division of Research, Kaiser Permanente Medical Care Program

## Endostatin and Cancer

Individuals with Down's Syndrome have little to no atherosclerosis and a significantly reduced cancer risk. These advantages seem to be mediated by the Syndrome's high serum levels of endostatin. Endostatin inhibits the formation and growth of blood vessels, a process called angiogenesis. Angiogenesis in the plaques of atherosclerotic vessels can lead to acute myocardial infarction, and angiogenesis is also essential for tumor sustenance and growth. Our research asked: Is there an inverse association between serum levels of endostatin and risk of cancer? The study used serum from 212 individuals who subsequently developed some type of solid tumor (and controls) and found that the risk of cancer was increased by 25% for those in the lowest quartile of endostatin levels compared to those in the highest quartile. However, this inverse relationship only held true for men (especially Asians), making clear the need for further research. *Submitted for publication.*

*A low level of endostatin is associated with a 25% increased risk of cancer in men, especially Asian men. But high levels of endostatin are not protective; in fact, in this study, above-low levels of endostatin did not appear to convey decreased cancer risk for anyone.*

ST Herrinton LJ, Iribarren C, Darbinian JA, Malinowski D, Tamarkin L, Vogelman JH, Orentreich N, Baer D.
Relationship of serum endostatin, an endogenous anti-angiogenic protein, with risk of cancer in the subsequent 36 years.

Collaborators: Division of Research, Kaiser Permanente Medical Care Program; CytImmune Sciences, Inc; and Department of Oncology, Kaiser Permanente Oakland Medical Center

# Studies in Progress

## Aging

### Alzheimer's Disease

The goal of much Alzheimer's Disease (AD) research is to develop specific and sensitive blood tests that can detect very early AD when therapy might be most effective as well as to identify or validate risk factors for this and other dementias. One of our studies concerns:

ST Proteomic Profiles (Proteomics is the analysis of the expression, localization, function, and interaction of the proteins expressed by the genetic material of an organism.) Proteomic profiles have been used to identify serum proteins associated with AD. Our study uses the advanced and refined combination of Difference Gel Electrophoresis (to precisely and quantitatively compare samples) and then Mass Spectrometry (to identify differently expressed proteins).

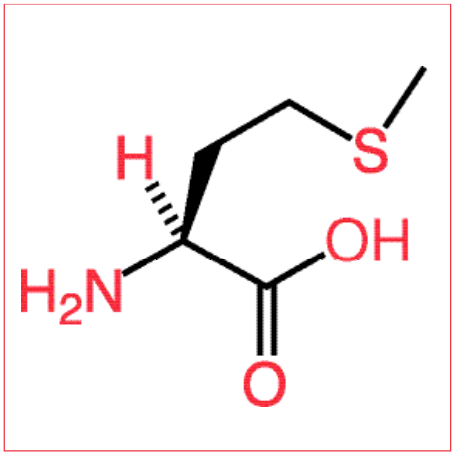
Collaborator: Department of Pediatrics, University of Colorado School of Medicine

### Dietary Interventions

*For details on Calorie Restriction and Lifespan Extension, see* VitaLongevity, *March 2005 at <www.orentreich.org>.*

Both methionine restriction (MR) and calorie restriction (CR) extend the lifespan of rodents, but MR extends lifespan without any restriction of calories. Our question is:

MR Is the lifespan extending effect of CR due to *de facto* restriction of the amino acid methionine?




**Structure of Methionine**

### Gene Expression

Gene expression studies look for genes being turned on or turned off (or not affected) by a disease, drug, treatment, carcinogen, etc. Micro-arrays of RNA from the tissue of interest are analyzed. Using tissues from young and old rats, our questions are:

MR What are the effects of CR on gene expression in heart and adipose tissue?

Collaborators: LifeSpan BioSciences, Inc; and Department of Pathology, University of Washington

MR What are the effects of MR and CR on gene expression in adipose, liver, and muscle tissues? The results will supplement our research published in 2006 on these same animals regarding energy balance measures, adipose tissue weights, and a variety of blood chemistries.

Collaborator: Pennington Biomedical Research Center

### Oxidative Stress

Free radicals are molecules with one or more unpaired electrons, a chemical situation that results in their being highly reactive, either losing (the process of oxidation) or gaining (the process of reduction) an electron to attain stability. Although dubiously received when proposed in the 50s, considerable evidence now supports free radicals having a very important role in biological aging. Pro-oxidants damage lipids, DNA, proteins, and cellular defense systems, which are composed of anti-oxidants (reductants). The right balance between oxidative and reductive forces is key; for example, too much oxidation results in cataracts and skin wrinkling.

The amino acid methionine is highly sensitive to oxidative damage, but this damage can be repaired by methionine sulfoxide reductase (MSR). Higher levels of MSR correlate with longer lifespan, and CR is known to increase MSR expression. Our research asks:

MR Does MR increase repair of oxidative damage or reduce oxidative stress?

MR Are serum thiol levels (high levels broadly indicate less oxidative damage) affected by either MR or CR?

# Plasmapheresis

As described in the 2005 Report, OFAS has embarked on a broad inter-laboratory project to determine the preventive and/or corrective effects of plasmapheresis on aging. Two research avenues are being pursued, one *in vitro,* the other *in vivo.*

## *In Vitro* Studies

**Effect of Plasmapheresed Serum on Cells Grown in Culture**

These will be demonstrated with the following steps:

- establish a cell system for study, *i.e.,* determine whether rates of cell proliferation and death for various cell lines can be manipulated in the presence of, for example, Epidermal Growth Factor and Transforming Growth Factor
- evaluate effect of whole and fractionated serum from rats of different ages
- apply proteomic and metabolomic techniques to identify factors in serum that enhance or limit growth
- evaluate whole and fractionated serum from rats that have been plasmapheresed
- apply proteomic and metabolomic techniques to identify factors in serum from plasmapheresed rats that enhance or limit lifespan

## *In Vivo* Studies

**Effects of Plasmapheresis on Various Bio-Parameters**

In the past year our efforts have focused on evaluating a host of bio-parameters to delineate those that would give reliable, pertinent, strong data for a Biological Aging Score (BAS) relevant to the well-characterized strain of rat being studied. The selected parameters include core body temperature, features of nail and hair growth, activity level, collagen strength, and various measures of biochemical oxidative stress and cognition; also included are basic and special tests related to hematology and immunology.

**Refinement of Plasmapheresis Technique**

Contemporaneous with developing the BAS, all aspects of the plasmapheresis technique were honed and refined so that the overall research would not fail to produce results because of some methodological flaw. One significant improvement was in the anesthesia system that now allows the plasmapheresed rats to be thoroughly at ease with just light anesthesia; the previous method required deep anesthesia, which confounded some of the biochemical test results and occasionally caused accidental death.

# Data Mining

**Reference Ranges** for common and not-so-common laboratory blood test results are being, respectively, refined and developed by analytic data-mining of vast databases of test results. These reference ranges will show the changes that do or do not normally occur with sex and age. Analyses are in progress for basic tests in the categories of hematology, chemistry, lipidology, and endocrinology, and some special analytes.

**Multi-Analyte Profiles** that have been generated in the course of other research are being analyzed for indications of changes with sex and/or age.

**Seasonal Effects** on hormone levels are being examined to see if the effects of season vary with age and sex.

*For why it is important to track your own tests results over time, and useful to have a reference range, see* VitaLongevity, *December 2004 at <www.orentreich.org>.*

*For detailed information on Multi-Analyte Profiling, see* VitaLongevity, *September 2004 at <www.orentreich.org>.*

# Studies in Progress

## Cancer

### Breast Cancer

ST Proteomics is the analysis of the expression, localization, function, and interaction of the proteins expressed by the genetic material of an organism. Will proteomic profiling of serum from women who later developed breast cancer identify candidate proteins predictive of breast cancer risk?
Collaborators: Division of Research, Kaiser Permanente Medical Care Program; and Department of Endocrinology and Public Health, Albert Einstein College of Medicine

### Non-Hodgkin's Lymphoma

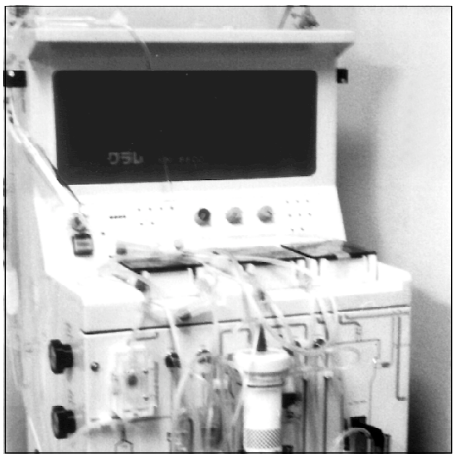
Three large epidemiologic studies are in progress to evaluate the relationship of this lymphoma to:

ST **Environmental Contaminants Such as DDT and PCBs**

ST **Infection with Epstein-Barr Virus**

ST **Cytokines and Other Growth Factors**

Collaborators: Division of Research, Kaiser Permanente Medical Care Program; and National Cancer Institute of the National Institutes of Health



**A machine for ultrapheresis treatment.**

### Treatment of Metastatic Cancer

The therapeutic effect of ultrapheresis, a method of selective plasmapheresis, will be evaluated in dogs with advanced cancer that is otherwise untreatable. The repetitive procedure involves having units of blood removed, selectively cleansed of pro-cancer factors, and reinfused.
Collaborators: School of Veterinary Medicine, University of Pennsylvania; and Animal Cancer Foundation, Veterinary Oncology & Hematology Research Fund

## Glucose and Diabetes

### Diabetes and Methionine Restriction

Type II Diabetes is assuming epidemic proportions, and the Goto-Kakizaki (GK) rat, a strain bred to develop Type II Diabetes, is a remarkably useful animal model for this disease. We hope that our research with the GK rat can ameliorate the growing crisis. We are asking:

MR Do rats with Type II Diabetes fare better on MR?

*For further information, see* VitaLongevity, *March 2005 and June 2005 online at <www.orentreich.org>*

### Glucose Metabolism and Methionine

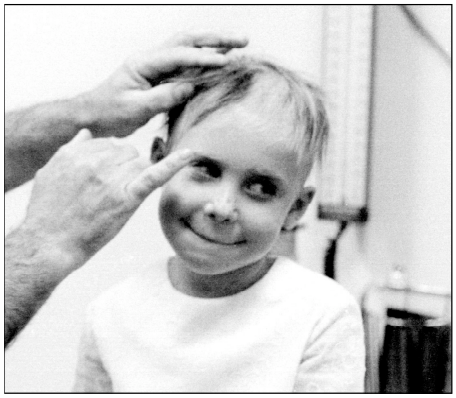
Increasingly impaired ability to control glucose levels (because of inadequate insulin) is an established biomarker of aging. With our research showing various benefits of MR, we wondered about its effects on glucose/insulin metabolism and are asking:

MR Does MR beneficially affect glucose/insulin?

## Hair

### Alopecia Areata

This type of hair loss can take many forms, from a small patch to loss of every hair; it spares no age group. Our studies try to ferret out possible causes and/or co-factors. Currently these involve:



**Multi-Analyte Profiles (MAP)** of serum from children and adults with various forms of alopecia areata (and controls). (For detailed information on Multi-Analyte Profiling, see *VitaLongevity,* September 2004 at <www.orentreich.org>.)
Collaborator: Rules-Based Medicine, Inc

**Serum Analysis** of promising analytes turned up by MAP testing. Analyses of adult sera are still to be done, but Leptin and Interleukin-18 are interesting findings in children. Additional samples are being sought to enhance the statistical validity of our findings.

**Antibodies to Infectious Agents** are being looked for in biopsy specimens because infection is a possible co-factor. This lead came from MAP testing, which detected a higher than expected frequency of some antibodies to several common pathogens.
Collaborator: Rules-Based Medicine, Inc

## Obesity

### Methionine Restriction (MR)

Methionine is an essential amino acid required to sustain life; it must be acquired from dietary sources because the body cannot make it. Many years of OFAS research have uncovered a number of benefits (typically demonstrated in rodents) from a diet very low in methionine but still sufficient to maintain good cell/tissue/organ function. The effects of MR are remarkably similar to those of a severely calorie-restricted (CR) diet. In addition to lifespan extension and disease reduction, one of the features of MR is the absence and/or prevention of adiposity. Our research is focused heavily on the effects of MR on adiposity and adipose tissue metabolism.

MR Will obese human beings lose weight on a full-calorie diet with only the methionine component restricted?
Collaborators: Pennington Biomedical Research Center; and Ross Products Division, Abbott Laboratories

MR Is the anti-obesity effect of MR related to energy expenditure?

MR Is the anti-obesity effect of MR due to its effect on specific hormones and enzymes within adipose tissue?

# OFAS-KP Serum Treasury

## UNIQUE RESEARCH RESOURCE

The Serum Treasury—combined with the number-identified donor's previous and subsequent medical histories—offers a unique opportunity to discover disease risk (or prevention) factors that are detectable in serum and to do so by the time-efficient and cost-effective method of *retrospective epidemiology.*

In 1964, the Kaiser Permanente Medical Care Program (KPMCP) established a system of regular and comprehensive broad-spectrum physical examinations, including blood testing and urinalysis, with the goal of providing improved health maintenance through early diagnosis. Health, disease, and epidemiologic data on participants were computer-databanked. A foresighted aspect of the program was freezing a 2 mL sample of serum from each participant for future research purposes.

Between 1964 and 1971, some 263,000 serum samples were collected and stored on nearly 123,000 multiphasic health examinees, each of whom had fasted for 12 hours and had had blood drawn one hour after a 75 gram oral glucose load. The following tests were routinely performed: cholesterol, glucose, creatinine, calcium, total protein, albumin, uric acid, and serum glutamic oxaloacetic transaminase (SGOT). Each sample was labeled with an identification number and the donor's sex, date of birth, and date of sampling.

By the late 1970s, storage of these uncataloged samples was becoming a space and special freezer facility problem. (The collection had been maintained at -30°C until June 1969 and at -25°C thereafter. After arriving at OFAS in 1980 the original 263,000 samples and all subsequent additions have been maintained at -40 ± 2°C.)

At the behest of Alyce A Kaiser and the two conceptors of the collection, Drs Sidney Garfield and Morris F Collen, OFAS assumed custody after first validating the chemical integrity of this incipiently valuable research resource.

Then came the computer cataloging of each sample so that any given sample could, in fact, be retrieved. Thus was created the Serum Treasury that—with the medical databank already managed by KPMCP—came to be described by the World Health Organization as *"among the most valuable resources currently available in biological banking".*

After 1984, OFAS added 119,500 samples from then current members of KPMCP; of these, 113,185 are from donors to the 1964-1971 collection.

The potentially confounding factor in research with the Serum Treasury is desiccation of samples. This has been successfully addressed by normalizing any data to the serum's sodium level if such sodium level is outside the 99th percentile limit of sodium (135-153 mmol/L).

To date, there have been 32 Serum Treasury studies published and several more are in press or in the manuscript preparation stage.

The Serum Treasury has become the productive research resource it is today because of the dedicated efforts of our staff and consultants, our many excellent collaborators, the expertise and cooperation of the epidemiology research staff at KPMCP, and, of course, the support of generous and faithful contributors to OFAS.

*The preceding is only a brief summary of the evolution this Serum Treasury, as well as basic information critically pertinent to researchers. Details are available at <www.orentreich.org>.*

## ATTENTION RESEARCHERS

If you have a research question relating to a human disease or disease prevention factor for which there is adequate scientific evidence of a serum marker to justify use of the OFAS-KP Serum Treasury in pursuit of a definitive answer, please submit your proposal for consideration to:

## OFAS

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Cold Spring-on-Hudson,
NY 10516-9802
Tel: 845.265.4200
Fax: 845.265.4210
E-mail: ofas@orentreich.org

# OFAS-WHO Serum Treasury

In 2006 OFAS received an incredible offer from the National Cancer Institute (NCI) to acquire a truly historic and unique repository, the World Health Organization (WHO) Serum Reference collection. Drs John R Paul and Alfred S Evans of Yale University School of Medicine's Department of Epidemiology and Public Health, past collaborators with OFAS, collected these sera in the 1960s and 1970s from interesting populations in diverse areas of the world. These irreplaceable specimens have rich associated data and should prove invaluable for future scientific research.

A large number of tests for various infectious agents, *e.g.,* poliomyelitis, human T-cell leukemia virus type 1, Chagas, *Mycoplasma pneumonia,* and para influenza 1-3, were carried out on these sera. For example, one study collected sera from military recruits at both entrance into and completion of military service in Argentina, Brazil, Columbia, and the United States and compared the incidence of acute respiratory and other infections in these populations. Another example, closer to home, involved West Point cadets and was a 4-year prospective study of infection with Epstein-Barr virus and the occurrence of infectious mononucleosis; the published results reported interesting psychosocial risk factors in the development of infectious mononucleosis.

OFAS received this collection on September 20, 2006, from NCI, where it had been stored since 1990. We have much work to do to bring the records up to date and into a modern-era computer format to facilitate its use.

In total, the repository comprises 20 sub-collections of sera representing individual studies, each of which generated several publications. We look forward to reporting the results of studies that originate at OFAS utilizing the OFAS-WHO Serum Treasury.

# PAST

The Pet Animal Serum Treasury (PAST) is a project of the Animal Cancer Foundation and OFAS and is the only resource of its type for animals in the world. Started in 2003, it is dedicated to improving veterinary care by collecting and archiving blood (serum) specimens from diseased and healthy pets, typically cats and dogs. As with the Serum Treasury maintained by OFAS and its related database maintained by Kaiser Permanente Medical Care Program, PAST will serve as a unique resource for research into the causes of or potential risk factors for cancer and other diseases in pets.


PAST samples will be used to see if any serum factors are present in pets that can predict or identify diseases in their earliest stages. The database contains information on the pet, its environment and eating habits, and veterinarian reports pertaining to its condition and treatments; over 40 different parameters are collected for each animal, and any combination of data can be searched for and retrieved in seconds.

PAST contains over 1000 samples collected from cats living in a free-range shelter and from dogs and cats that visit an oncology clinic. The Dalmatian Club of America also participates by collecting samples at regional shows. We are currently looking for additional donation sites. For further information, go to <www.orentreich.org>.

# *VitaLongevity*™ Newsletter

*OFAS started the quarterly* VitaLongevity *newsletter in June 2004 to alert friends to those health strategies that are valid and those that are not valid, as well as to offer new suggestions for making their lives as long and healthy as possible.*

**Abdominal Obesity (December 2006)**
Visceral obesity, excess fat deposited in the deep abdominal area, poses many health risks. As a key component of the Metabolic Syndrome, visceral fat functions like an endocrine organ by secreting substances that negatively affect the liver, pancreas, and other organs. This issue explains how visceral fat contributes to the risk of diabetes, cardiovascular disease, and even some types of cancer through release of these harmful circulating mediators.

**Anti-platelet Resistance (September 2006)**
Aspirin achieved super-status in the pharmaceutical hall of fame when it became known as the single most important drug for the prevention of heart attack and stroke. Aspirin and other drugs such as clopidogrel (Plavix®) do this by preventing clumping of blood platelets, although they achieve the result by different mechanisms. Recent research and clinical observation have shown that some persons are not benefited by these drugs, that is, they are resistant to anti-platelet therapy. The two types of resistance are discussed along with the availability and reliability of tests for resistance, test interferers, and possible circumventions to overcome resistance. Annual testing (using the same test method) is a good idea since resistance can develop over time.

**Infections and 'Unrelated' Disease (June 2006)**
Recent groundbreaking research has uncovered links between an astonishing variety of infectious agents and subsequent diseases, from reactive arthritis being linked to food-borne infections to obesity being linked to Adenovirus 36. Infectious agents, ranging in size from sub-cellular viruses to multi-cellular parasites, can turn a cell cancerous either through years of chronic inflammation/irritation or by direct cell transformation. Topics covered: covert infections; infections and cancer; infections and autoimmune diseases, including neuropsychiatric disorders; and awareness and prevention.

**Frailty (March 2006)**
This issue of the newsletter discusses the relatively new concept of frailty as a distinct clinical state with measurable components that can predict adverse health outcomes, *e.g.,* falls, disability, hospitalization, and even death. Three or more of the following characteristics constitute frailty: unintended weight loss of >10 lbs in a year; low muscle mass and weakness; fatigue/exhaustion; slow walking pace; and low physical activity. Pre-frailty (any two components) carries a high risk of becoming frail and an intermediate risk of adverse health outcomes. The components and counteractive measures are discussed.

## Previous Issues

**DHEA and DHEAS** December 2005

**Vitamin D** September 2005

**Glucose Toxicity** June 2005

**Calorie Restriction and Lifespan Extension** March 2005

**Mapping the Present** December 2004

**Mapping the Future** September 2004

**Biotin** June 2004

All *VitaLongevity* newsletters are available in PDF format at <www.orentreich.org>.

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