

OFAS

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

Report of the Directors

Dear Friends, Supporters, and Fellow Researchers,

It will come as no surprise to regular readers of our yearly Reports that OFAS research continues on the longevity-enhancing effects of a diet low in the essential amino acid methionine. This year saw the publication of our research showing that this diet alters the balance of lipid buildup and breakdown within the fat cells of rats. Two other papers are in preparation concerning the ability of rats on this diet to resist weight gain despite excess calorie intake and the mechanism by which this phenomenon takes place.

Readers will more directly appreciate the potential results of a nearly completed study in collaboration with Pennington Biomedical Research Center at Louisiana State University. This study will determine if a methionine-restricted diet influences desired weight loss and reduces insulin resistance in persons meeting the clinical criteria for Metabolic Syndrome, a frequent precursor of Type II diabetes.

OFAS continues to make productive use of its Serum Treasury in collaboration with the Kaiser Permanente Medical Care Program. Three studies are in progress to assess potential risk markers for liver and breast cancers and novel biomarkers for acute myocardial infarction. This year also brought the publication of Serum Treasury research establishing that infection with *Helicobacter pylori* is not a risk factor for pancreatic cancer. Additionally, two publications resulted from our participation in collaborative re-analyses of data from 18 worldwide studies to clarify risk factors for prostate cancer. These publications are summarized inside.

Last year, we reported on the new clinical research division of OFAS, Therapeutic Silicone Technologies, Inc. (TST), formed for the development of therapeutic uses of highly purified silicones. TST does not manufacture or sell the therapeutic products; rather, it licenses proprietary technology for commercial distribution, using any proceeds to fund ongoing research, development, and clinical trials. As detailed inside, TST is preparing to seek FDA approval for a clinical trial to determine whether diabetic foot ulceration can be effectively prevented by silicone injections at ulcer-prone sites. Prevention is important because foot ulceration is the primary cause of lower extremity amputations among diabetics.

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

With appreciation for the efforts of our staff and collaborators and for your support and encouragement, we remain respectfully yours,

Norman Orentreich, MD, FACP
Founder and Co-Director

David S Orentreich, MD
Co-Director

Prevention of Foot Ulcers

The OFAS applied research division, Therapeutic Silicone Technologies, Inc., is in the process of submitting an application to the FDA to evaluate treatment with injections of liquid injectable silicone (LIS) to prevent ulceration in patients with a history of foot ulcers due to diabetic neuropathy.

Nerves that carry information about pain and temperature are often selectively attacked in diabetic neuropathy. Patients with this condition lose the “gift of pain” that would make them aware of chronic and acute foot traumas that can ultimately ulcerate. Few persons realize that diabetic foot ulcers account for 60% of non-traumatic lower extremity amputations—a shocking 71,000 in a single year (2004) in the USA!



Photo courtesy of Lawrence Lavery.

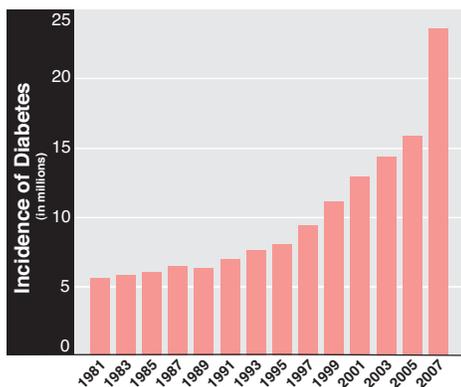
Dr. Lawrence Lavery, DPM, MPH

“There are very few innovative options to prevent foot ulcers. The technique to improve soft tissue padding on the foot to prevent foot ulcers has the potential to prevent ulcer recurrence and thousands of amputations a year.”

The clinical trial using LIS to prevent diabetic foot ulcers will be conducted under the direction of Dr. Lawrence Lavery, DPM, MPH, of Scott and White Healthcare. Scott and White is one of the nation’s largest multi-specialty healthcare systems, with more than 500 physicians caring for patients throughout central Texas. Dr. Lavery is a world-recognized leader in diabetic foot care, publishing and lecturing extensively on the topic. He and a colleague were recently awarded an NIH grant of \$2.3 million for research related to the diabetic foot, the largest NIH grant ever won by podiatrists. OFAS is delighted to have someone of Dr. Lavery’s vast experience in treating diabetic feet directing this clinical trial.

The trial is anticipated to demonstrate that treatment with LIS reduces pressure and shear forces, both of which are key factors in ulcer development, by providing padding between skin and bone. Dr. David Orentreich will personally train Dr. Lavery in the LIS treatment technique. The treatment group will receive LIS injections into areas subject to high pressure/shear forces. These patients will be compared to others receiving standard care, which consists of a visit to a foot specialist every three months for evaluation of foot pulses and sensitivity, nail and callus treatment, and counseling on foot care, including custom shoes to reduce forces that can lead to ulcers.

Dr. Orentreich has shown Dr. Lavery the extraordinary clinical efficacy of LIS by introducing him to one of his patients who had been unable to walk after having lost virtually all of his feet’s soft tissues from HIV-associated lipoatrophy; treatments with LIS restored ambulation by providing essential cushioning.



Nearly 8% of the US population is diabetic, a 400% increase between 1980 and 2007, according to recently released CDC data. Among the now 23.6 million diabetics, there is a 15-25% lifetime risk of developing a disabling foot ulcer, of which some 28% will re-ulcerate within a year, and nearly 100% within three years.

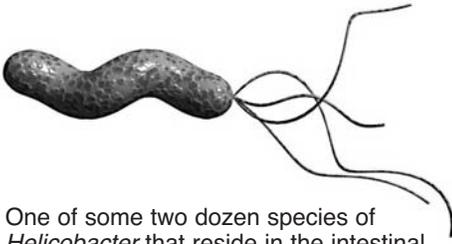
If the study is successful, OFAS will have provided those who care for diabetic patients with a unique and effective treatment to prevent one of the most dreaded complications of diabetes: disabling foot ulcers with the potential for lower extremity amputation.

Further information about Therapeutic Silicone Technologies, Inc., can be found at www.orentreich.org/tst.htm.

Source: Centers for Disease Control and Prevention (CDC)

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

Pancreatic Cancer and *Helicobacter pylori*



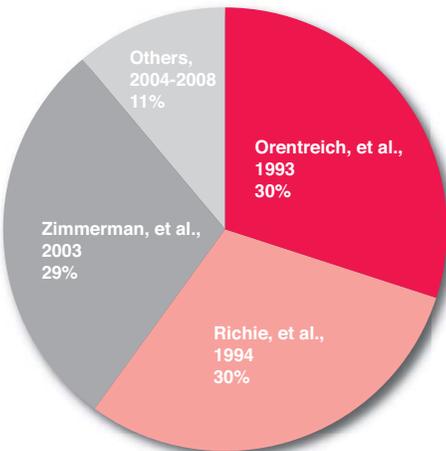
One of some two dozen species of *Helicobacter* that reside in the intestinal tract of animals and human beings, *H. pylori* is between 2.5 and 5.0 microns long and lives beneath the mucus layer of the stomach.

Courtesy of Luke Marshall, Helicobacter Foundation

In 1994, the *Helicobacter pylori* bacterium was declared a human carcinogen by the International Agency for Cancer Research. Its causal associations with gastric cancer and gastric lymphoma have been well established, in part by OFAS studies. Some preliminary studies have suggested *H. pylori* might be involved with pancreatic cancer, the fourth leading cause of cancer death. To test this hypothesis, we used the OFAS-Kaiser Permanente Serum Treasury to look for antibodies to *H. pylori* (indicating previous infection) in the sera of 104 persons who later developed pancreatic cancer and 262 persons who did not. We found that the risk of pancreatic cancer was not increased by this bacterial infection. Additionally, our study confirmed that smoking increases risk and that risk was not affected by alcohol consumption or body mass index.

ST de Martel C, Llosa AE, Friedman GD, Vogelmann JH, Orentreich N, Stolzenberg-Solomon RZ, Parsonnet J
Helicobacter pylori infection and development of pancreatic cancer. *Cancer Epidemiology, Biomarkers and Prevention* 2008; 17(5):1188-94.

Methionine Restriction



Research papers (164) citing 6 OFAS publications on a methionine-restricted diet.

Our previous studies have shown that rats fed a methionine-restricted (MR) diet gain several advantages over those fed standard chow, including living 40% longer and being resistant to obesity despite consuming more calories per gram of body weight than rats fed ordinary chow. We hypothesized that the rats' adrenal hormone corticosterone might be involved because corticosterone increases the number and size of rat fat cells.

This study examined various fatty tissue sites for their corticosterone content. MR increased their levels of corticosterone but, unexpectedly, reduced fat cell size. Knowing that fat cell size is a balance between the buildup and breakdown of lipids within the fat cells, we examined this balance. We found that MR increased lipid breakdown but surprisingly increased lipid buildup, suggesting that MR induced a 'Futile Cycle', in which two metabolic pathways run simultaneously in opposite directions with no overall effect other than wasting energy. This might be the key to how MR rats stay lean on a high calorie diet.

Perrone CE, Mattocks DAL, Hristopoulos G, Plummer JD, Krajcik RA, Orentreich N
Methionine restriction effects on 11 β -HSD1 activity and lipogenic/lipolytic balance in F344 rat adipose tissue. *Journal of Lipid Research* 2008; 49(1):12-23.

Prostate Cancer

Because of our previous research on prostate cancer using the OFAS-Kaiser Permanente Serum Treasury, OFAS was part of the Endogenous Hormones and Prostate Cancer Collaborative Group's re-analyses of data from 18 prospective studies on risk factors for prostate cancer.

One study of 3671 prostate cancer cases and 5212 controls concluded that the higher the concentration of, specifically, Insulin-like Growth Factor-I, the higher the risk for prostate cancer, although the risk was only moderately increased. The other study of 3886 cancer cases and 6438 controls concluded that serum concentrations of sex hormones were not associated with prostate cancer risk.

ST Roddam AW, Allen NE, Appleby P, *et al.*
Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies. *Annals of Internal Medicine* 2008; 149(7):461-71, W83-8.

ST Endogenous Hormones and Prostate Cancer Collaborative Group
Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *Journal of the National Cancer Institute* 2008; 100(3):170-83.

Methionine Restriction Collaborations

Animal



Virginia Malloy (Director, OFAS Biological Sciences Lab) and Thomas Gettys (Chief, Pennington Division of Experimental Obesity)

OFAS has demonstrated that rats fed a methionine-restricted (MR) diet live on average 40% longer than their control-fed (CF) counterparts. Interestingly, MR animals also have lower body weight and limited fat accumulations despite higher calorie intake per gram of body weight than CF animals.

In collaboration with Dr. Thomas Gettys of the Laboratory of Adipocyte Signaling at Pennington Biomedical Research Center (Louisiana State University, Baton Rouge, LA), OFAS is studying whether MR rats resist weight gain because they convert the calories from their high food intake to heat. We are addressing this question in young, adult, and old animals using indirect calorimetry. With this technique, we measure heat production (energy expenditure) continuously over 72 hours, as well as the selected source of calories (protein, carbohydrate, fat) of both MR and CF rats. The 72 hours comprises three 24-hour periods of peak activity and feeding (night) and low activity and sleep (day). Should, as we suspect, MR animals exhibit enhanced energy expenditure compared to CF animals, additional studies will follow to explore the underlying mechanism(s), which might be related to a metabolic 'Futile Cycle', about which OFAS has recently published (see page 3).

Human



Frank Greenway (Chief, Pennington Outpatient Clinic Unit) and Carmen Perrone (Director, OFAS Cell Biology Lab)

Because OFAS has shown that a methionine-restricted (MR) diet in rodents is effective at reducing weight gain and improving insulin responsiveness, a Phase I Clinical Trial using MR in obese human adults meeting the Adult Treatment Panel III (ATP III) criteria for Metabolic Syndrome has been conducted in collaboration with Dr. Frank L. Greenway of the Pennington Biomedical Research Center.

The objective of the study was to determine whether the MR diet could reduce weight and thus improve insulin resistance in these subjects. The study assigned subjects to 16 weeks of either the MR diet, containing 2 mg/kg/day methionine, or a control diet, containing 35 mg/kg/day methionine. Changes in insulin sensitivity, body fat mass, and serum analytes, as well as weight and energy expenditure, were among the parameters used to monitor MR-induced changes. Data analysis is currently underway.

INFORMATION FOR DONORS

The Orentreich Foundation for the Advancement of Science, Inc. was founded in 1961. OFAS is a non-profit institution dedicated to biomedical research to prevent, halt, or reverse those disorders that decrease the quality or length of life. A 501(c)(3) non-profit corporation (EIN 13-6154215), OFAS is duly registered with the United States Internal Revenue Service as an Operating Private Foundation under Section 4942(j)(3).

No accomplishment of OFAS is possible without your encouragement and generous support. Your tax-deductible contribution should be mailed to:

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