



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

Report of the Director

Microorganism-Disease Links

- *Borna Disease Virus* & psychiatric mood disorders
- Various viruses & atherosclerosis
- *Chlamydia pneumoniae* & Alzheimer's Disease
- Foodborne bacteria & arthritis
- Bacteria & kidney stones
- *Parvovirus* & polyarthralgia syndrome

As the year closes, we would like to share with you our 1998 accomplishments. Recently completed contributions to the scientific and medical communities, published in such prestigious journals as *Science*, are listed on the back cover. As important, however, are those sections about on-going research. Open to the next page and find listed our current studies, both in-house and collaborative. All reflect our enduring goal – to prevent, halt, or reverse those disorders that decrease the quality or length of life.

Toward that goal, two areas of current research of particular interest are heart disease and diabetes. These diseases are under intensive investigation worldwide, but, as you will see, research at OFAS has an uncommon perspective.

Heart Disease: Our interest is part of a small but growing international awareness of the obscure role of previous infection with an apparently unrelated disease. We ask: What is the relationship of prior infection with the microorganisms known as *Helicobacter pylori*, *Chlamydia pneumoniae*, and *Cytomegalovirus* to subsequent heart disease? Our Serum Treasury will be as useful in answering this question as it was in firmly establishing the links between *Epstein Barr Virus* and Hodgkin's Disease, and between *H. pylori* and common stomach ulcers and GI malignancy.

Diabetes: Tremendous breakthroughs (see Conferences inside) have been made in the understanding, and thus the treatment, of diabetes with its wide variety of effects and symptoms. Pairing our expertise in the biology of skin with emerging insights into the molecular and cellular mechanisms of diabetes, OFAS is investigating glucose metabolism and insulin resistance in the skin of diabetics and 'prediabetics' in relation to those skin conditions they tend to experience, including generalized accelerated aging of the skin.

With our appreciation for your interest and support – and with best wishes for success in the coming year.

Norman Orentreich, MD, FACP

In-House Studies in Progress

Aging

- Methionine-restricted diets to increase median and maximum lifespans
- correlation of proteinuria to kidney disease
 - effect on glutathione levels of the choice of which non-essential amino acid substitutes for the essential amino acid methionine

Autoimmune Skin Diseases

- Alopecia areata and vitiligo
- identifying and isolating alopecia areata-related antigens
 - testing for presence of hair-related auto-antibodies in human serum
 - assessing durability of cultured melanocytes grafted into vitiliginous skin
 - improving the mouse model for alopecia areata
 - evaluating effects of steroids on pigment-forming cell function

Diabetes and Skin

- In naturally obese mice
- monitoring the progression of acanthosis nigricans in males and females
 - determining sex differences in the levels of insulin, glucose, IGF-1, C-peptide, androgens, estrogens, and corticosterone
 - evaluating the effect of high-fat and high-fructose diets on the induction of insulin resistance

Role of hyperinsulinemia and insulin resistance in granuloma annulare, skin tags, and acanthosis nigricans in human beings

Hair and Sebaceous Glands

- Effect of oral or topical administration of 5 α -reductase Type I inhibitors and HMG-CoA reductase drugs on
- hair growth in the long-haired Syrian hamster, the OFAS model for human hirsutism
 - hair loss in the OFAS balding mouse model for human androgenetic alopecia
 - oil production by hamster ear sebaceous glands, the OFAS model for sebum production in acne

Metabolism of testosterone by skin

- evaluating the difference between strains of mice that do or do not exhibit androgenetic alopecia
- analyzing the effect of androgen administration on testosterone-metabolizing enzyme activity

Major distinctions between balding and non-balding human scalp tissue at the cellular, enzymatic, and molecular levels

- differences in histochemical parameters
- differences in activities of 5 α -reductase Types I and II
- differences in mRNA

Effects of natural and inhibited programmed cell death (apoptosis) on hair follicles prone or resistant to balding

Effect of growth factors (IGF-1, IGF-2 and FGF-2) on stem cell activity and human hair follicle performance *in vitro*

Effect of cholesterol-lowering drugs (statins) on human hair follicle growth *in vitro*

Effect of the anti-androgenic compound (EGCG) in green tea on rat prostate, sebaceous glands, and androgenetic alopecia

Conferences

Each year staff members attend various conferences and seminars exchanging information with other scientists in fields of mutual interest. Following are meeting highlights and brief descriptions of our related research.

Broda O Barnes, MD Research Foundation 1998 Annual Fall Conference

Stamford, CT
October 2-4, 1998

Summary by: RA Krajcik

The effects of chronic excess insulin on general health are widespread and not limited to conditions associated with glucose metabolism. Accelerated aging, cancer, arthritis, cardiovascular disease, hypothyroidism, and even autoimmune diseases have been linked to hyperinsulinemia. Nutritional approaches to controlling or balancing the body's production of the opposing hormones, glucagon and insulin, were discussed. Conventional wisdom that complex carbohydrates should comprise the bulk of daily caloric intake (e.g., the American Diabetic Association diet guidelines) was challenged, because such a diet encourages excess insulin secretion. Controversially, it was instead reported that a good balance of insulin and glucagon can be achieved by a calorie-restricted dietary program that provides adequate levels of protein in each of three meals and two snacks daily – the ideal protein:carbohydrate:fat calorie ratio being 3:4:3. Controlled studies involving Type II diabetics following such a diet showed improvements in blood glucose, insulin, triglycerides, and fat mass. The cutaneous manifestations of hyperinsulinemia studied by OFAS should be responsive, at least in theory, to such dietary interventions.

80th Annual Endocrine Society Meeting

New Orleans, LA
June 24-27, 1998

Summary by: RA Krajcik

The syndrome of insulin resistance, also known as the metabolic syndrome, was the pervasive theme this year (as last year), because the effects of this condition – obesity, hypertension, blood lipid abnormalities, diabetes, and polycystic ovary disease – touch on every aspect of endocrinology. This common syndrome is believed to be caused by multiple interacting gene defects that vary between individuals and result in the variable clinical course. Last year brought the introduction of the first drug specifically designed to increase insulin sensitivity; it is now widely used, but patients must be monitored carefully for liver toxicity. OFAS research efforts involve monitoring the effect of such drugs on skin conditions related to insulin resistance, such as granuloma annulare and common skin tags.

10th International Congress on Hormonal Steroids

Quebec, Canada
June 17-21, 1998

Summary by: RA Krajcik

A broad range of topics was covered in depth including the endocrinology of menopause, prostate and breast cancer, androgen excess, and steroid enzyme inhibitors. A common theme in these discussions was the growing understanding of the complexities of steroid hormone action at the cellular level. The interaction, or cross-talk, between nuclear steroid receptors and cell-signaling pathways, as well as the recent discoveries of co-regulators of steroid receptors, make the job of designing hormonal therapies very challenging. A major on-going research interest at OFAS involves hormonal intervention in the androgenetic disorders of acne, hirsutism, and alopecia.

International Investigative Dermatology 1998 Conference

Cologne, Germany
May 6-10, 1998

Summary by: S Massardo

This third joint meeting of the American, Japanese, and European Societies for Investigative Dermatology was attended by more than 2000 distinguished scientists from around the world. The meeting boasted over 1400 abstracts representing the best of current research. Presentations included the latest developments in hair growth and acne control, plus gene therapy for a variety of skin disorders. Among the more exciting developments were the identification of a gene that may be responsible for alopecia universalis (a disease characterized by a complete loss of body hair), and new immunosuppressants to fight alopecia areata (a less severe form of the same condition). Also, researchers have identified a part of the hair follicle containing cells that may be useful for multiplying new hairs; these 'stem cells' are thought to provide the follicle with new hair-forming cells. Further study may lead to a better understanding of the signal(s) which turns these cells on and off. Researchers at OFAS are studying the interaction between stem cells and the actively growing parts of the hair follicle for clues to their role in this process.

Conferences

American Academy of Anti-Aging Medicine: 5th International Conference on Anti-Aging Medicine and Biomedical Technology

Las Vegas, NV
December 13-15, 1997

Summary by: RA Krajcik

2nd International Conference on Insulin Resistance – Novel Drug Development Strategies for Type II Diabetes and Obesity

Philadelphia, PA
October 6-7, 1997

Summary by: RA Krajcik

Conventional and unconventional approaches to the early detection and prevention of Alzheimer's Disease (AD) and the more common age-related decline in brain function were presented. Extensive neurophysical testing to determine the earliest detectable biomarkers for AD suggests metabolic changes precede both cognitive decline and structural changes in the brain. Memory enhancement by hormone replacement therapies and supplementation with vitamin E and phosphatidylserine, among others, show promise. Other presentations included truly astounding advances in cryopreservation both of organs for transplantation and of whole animals followed by resuscitation. OFAS has a long-standing interest in transplantation biology stemming from our Director's pioneering work in hair transplantation and, more recently, in the grafting of melanocytes to vitiliginous skin. The ability to cryopreserve human skin for a variety of future uses is a significant step forward.

Insulin resistance occurs when cells do not respond fully to normal or elevated amounts of circulating insulin, a situation that frequently leads to the development of Type II diabetes. Diabetes is expensive to treat, and the long-term complications can be devastating. Therefore, a major goal of current research is to understand the cause or the molecular mechanisms of insulin resistance which, in turn, may lead to drug therapies that actually prevent or delay the onset of diabetes. OFAS is currently investigating the cutaneous effects of insulin resistance, such as granuloma annulare, skin tags, acanthosis nigricans, and accelerated skin aging. The role of insulin resistance in Alzheimer's Disease was the focus of an OFAS collaboration with New York University School of Medicine published last year.

Seminars at OFAS



Rozlyn A Krajcik, RPh, PhD, Assistant Director – Scientific Affairs, has attended several conferences this year. Upon return, attendees share salient new findings and developments at staff meetings.

Biological Esterification of Steroids

Richard B Hochberg, PhD
Yale University School of Medicine
Dept of Obstetrics & Gynecology
New Haven, CT

Cutaneous Use of Cyanoacrylates

Leon Sun, PhD
Thor B Nielsen, PhD
SN Biotech, Inc
Rockville, MD

Comparison of Skin-Lightening Agents

Evelyn G Su, PhD
Sino Lion (USA) Ltd
New York, NY

Potential Medical Uses of Zwitterionic Buffers

T Ronald Theodore, MD
Integrated Biologics Research
Laboratories, Inc
Osterville, MA

Wound Healing

Ella S Lindenbaum, PhD
Israel Institute of Technology
Haifa, Israel

Collaborative Studies in Progress

ST Denotes studies using the OFAS Serum Treasury.

OFAS in collaboration with

| | |
|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| Prostate cancer and male hormone levels: Effect of religious or secular life style | Hadassah Medical Organization |
| T lymphocyte response to hair follicles in human subjects with alopecia areata | New York University School of Medicine |
| DHEAS and DHT: Their contribution to mortality differences in 1948 men and women aged 50 and over | Hadassah Medical Organization |
| ST Further analyses to see if DNA can be reliably found in serum samples | Kaiser Permanente Division of Research |
| Structure and molecular weight of the male sex-specific, cholesterol-like compound(s) in hamster ear sebum | Strang-Cornell Cancer Research Center |
| Identification of cDNA to locate hair-cycle-specific genes | New York University School of Medicine |
| ST The relation of prior infection with <i>Chlamydia pneumoniae</i> and/or <i>Cytomegalovirus</i> to subsequent heart attacks | Stanford University School of Medicine |
| ST Prior infection with <i>Helicobacter pylori</i> and later coronary heart disease | Stanford University School of Medicine |
| Ultrapheresis to remove Tumor Necrosis Inhibitory Factor to treat cancer | Tennessee Oncology Clinic |
| Comparative analysis of gene expression in balding and non-balding human hair | Life-Span BioSciences, Inc |
| Levels of IGF-1 as predictors of subsequent breast and prostate cancers | Kaiser Permanente Division of Research |
| Mechanism for delayed kidney disease in rats on a methionine-restricted diet | American Health Foundation |
| Anti-cancer effect of a taurine analog, a commonly used buffer in cell culture, on mice with spontaneous breast cancer or melanoma | Integrated Biologics Research Laboratories, Inc |
| Non-genomic effects of sex steroids mediated by SHBG and SHBG receptors | St Luke's-Roosevelt Hospital Center |

Analytic Advancements

Chromatography allows analysis of complex mixtures by separating them into individual components for identification and quantification. Recent advances in chromatography have improved the accuracy, detection ability, and speed of data acquisition and analysis. OFAS recently upgraded its equipment and data-management software for high-pressure liquid chromatography (HPLC) and for gas chromatography (GC).

HPLC with a Photodiode Array Detector separates and records the complete UV-visible spectrum of each eluant at each time point during a chromatographic run. Our new software, specialized to best acquire, store, and retrieve multi-wavelength data and complete spectra, makes our HPLC the ideal advanced analytic system for quality assurance and consistency of both research diets and test materials.

In GC, test materials are injected into a stream of inert gas, then passed through a coated capillary column with a resolving liquid phase; the adsorptive interaction between the components and the coating leads to differential separation of the mixture. GC has been particularly useful to OFAS in new developments for evaluating the effect of anti-androgens in the hamster ear sebaceous gland model for acne. OFAS hopes its enhancement of this model will allow researchers to use more humane and less invasive procedures.



Ho-meei Lin, PhD, at the updated HPLC.

Publications

ST Denotes studies using the OFAS Serum Treasury.

ST Association between high-density lipoprotein cholesterol and breast cancer varies by menopausal status.
Cancer Epidemiology, Biomarkers & Prevention 7:483-488, 1998

PG Moorman, BS Hulka, RA Hiatt, N Krieger, B Newman, JH Vogelman, N Orentreich

Known and suspected risk factors for breast cancer are associated with high HDL. Our study found no significant difference in HDL levels between 200 women with breast cancer and 200 matched controls. However, women who were pre-menopausal at date of cancer diagnosis had lower HDL than controls, whereas those post-menopausal at diagnosis had higher HDL. Thus, menopausal status is a consideration when analyzing risk factors for breast cancer.

ST IGF-1 and prostate cancer. (Technical Comment)
Science 282:199a, 1998 (<http://www.sciencemag.org/cgi/content/full/282/5387/199a>)

C Schaefer, GD Friedman, CP Quesenberry Jr, N Orentreich, JH Vogelman

This study of 45 men with prostate cancer and matched controls found no correlation between plasma Insulin-like Growth Factor-1 and risk of prostate cancer. Further analysis and/or data will resolve the apparent contradiction with a recent study of 152 pairs of cases and controls finding a 2.4-fold risk for men with the highest levels of IGF-1.

Effect of supplementation with chromium picolinate on antibody titers to 5-hydroxymethyl uracil.

European Journal of Epidemiology 14:621-626, 1998

I Kato, JH Vogelman, V Dilman, J Karkoszka, K Frenkel, NP Durr, N Orentreich, P Toniolo

Chromium picolinate, a popular dietary supplement for weight loss, damages chromosomes in cell culture, but an 8-week course of a typical dose (400 µg per day) did not increase DNA damage in human beings.

ST Gastrin and colorectal cancer: A prospective study.
Gastroenterology 115:275-280, 1998

CM Thorburn, GD Friedman, CJ Dickinson, JH Vogelman, N Orentreich, J Parsonnet

Colorectal cancer is the second leading cause of cancer mortality. Although above-normal serum gastrin levels were associated with a 3.9-fold risk, only 7% of those 250 cases studied had high levels, and the cancer was apt to be rectal. Also, in a few cases of colorectal cancer, there was a strong correlation with smoking. Of note: Gastrin levels are commonly elevated by use of acid-inhibitory medications, medications that are increasingly in use.

Interaction between a semisynthetic diet and indole-3-carbinol [I3C] on mammary tumor incidence in Balb/cfC3H mice.

Anticancer Research 17:4333-4338, 1997

VL Malloy, HL Bradlow, N Orentreich

Adding I3C to the diet delayed onset and decreased incidence of breast cancer; however, tumor incidence was also decreased in those fed standard diet, rather than an experimental diet high in ω-6 fatty acid. The beneficial effect I3C was most evident in mice exposed to it *in utero*. I3C is abundant in cruciferous vegetables.

INFORMATION FOR DONORS

Orentreich Foundation for the Advancement of Science, Inc, founded in 1961, is a non-profit institution dedicated to biomedical research. It is duly registered with the United States Internal Revenue Service as an Operating Private Foundation under Section 4942(j)(3).

Your tax-deductible contribution should be mailed to:

Orentreich Foundation for the Advancement of Science, Inc

910 Fifth Avenue
New York, NY 10021-4187

INFORMATION FOR 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 Serum Treasury in pursuit of a definitive answer, please submit your proposal for consideration to:

OFAS

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Scientific Affairs

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