



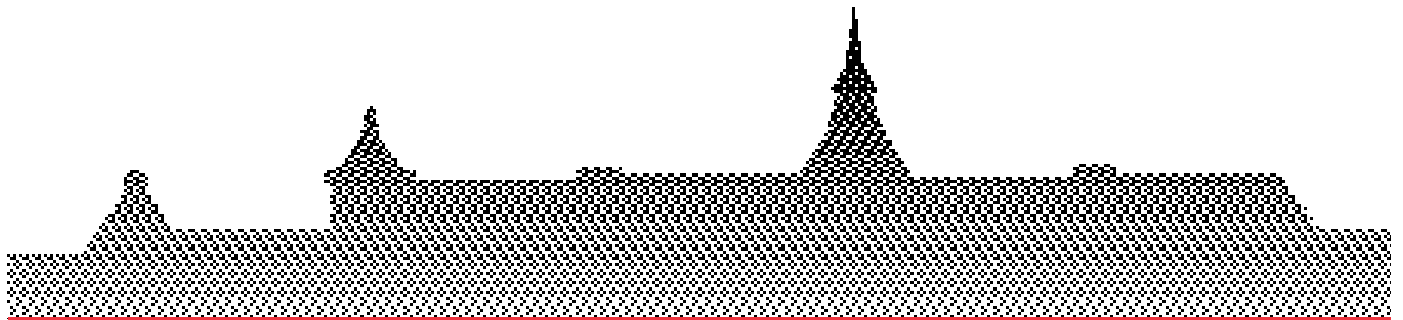
**F F A S**

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

**2001  
Report**



**Orentreich  
Foundation for the  
Advancement of  
Science, Inc.**



Biomedical Research Station

Cold Spring-on-Hudson, NY

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*Denotes studies using samples from the Serum Treasury.*

# Report of the Director

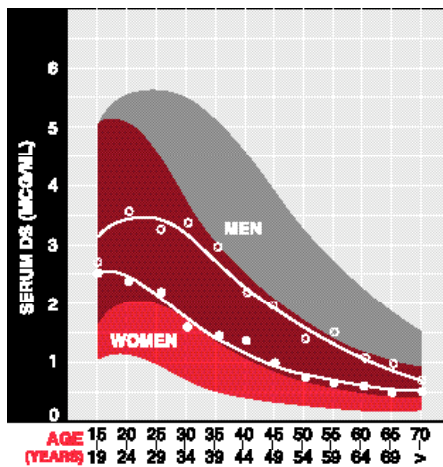
## The Composite Brain

Forty years ago most of us would have been amazed to hear that today computer programmers can solve immensely complex problems by combining a multiplicity of central processing units running individual specialized programs and integrating them into a coordinated, collaborative process.

Forty years ago, when OFAS was founded, it applied the analogous approach of combining the brainpower of a group of scientists with specialized skills to address the study of aging. The purpose: to measure biologic age vs. chronologic age and to determine those factors that accelerate, slow, or even reverse bio-age parameters. The evidence was clear that to measure bio-age one first had to determine the 'reserve' capacity (its performance under stress) of any specific organ system (heart, lung, etc.) and then evaluate the change over time of the interacting organ systems that compose the total organism.

To this end, OFAS assembled scientists from such diverse disciplines as biology, chemistry, biochemistry, medicine (human and veterinary), computing, engineering, and the emerging field of experimental gerontology.

Serum dehydroepiandrosteron sulfate in men ○ and women ● of different groups. The normal ranges are shown in ■ for women and in ■ for men.



## Focus & Diversity

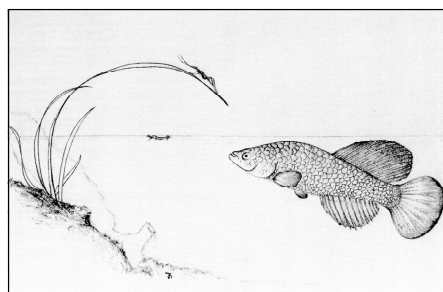
Over the years OFAS has determined various specific measures of bio-age, e.g., hair diameter, nail growth rate, keratin replacement. The most commonly cited contribution within the scientific community is the OFAS publication on the changes in levels of the major adrenal hormone DHEAS which goes up from puberty to adulthood and thereafter gradually down to senescence. This publication has become a primary reference against which bio-age-related studies correlate.

Composite brainpower allows for diversity as well as focus. For example, OFAS became involved in the blood-typing of George Washington (Type B, most likely) through samples of his hair, and in combating malaria in Sri Lanka with a special type of mosquito-eating fish that OFAS was using for aging studies; this fish can 'hibernate' in dried-up puddles and then re-emerge to eat mosquito larvae when the next rains fall.

## Research with the Serum Treasury

The acquisition and development in 1980 of what has become known as the Serum Treasury (see page 15 for a summary) was a seminal event in OFAS history. With it, OFAS expanded its scope to include looking at factors in serum that could prognosticate bio-aging or specific disease long before the eventuality. For example, scientists have the ability to evaluate the serological history of a cancer patient to see if factors that might have indicated the onset of the disease were present in blood drawn from routine doctor visits 10, 20, or even 30 years prior to the onset of the disease.

Throughout this Report research and papers utilizing selected specimens from the 500,000 units of the Serum Treasury are highlighted with the **ST** symbol. It is to be noted that important research results from Serum Treasury studies are, for the most part, the results of productive collaborations with both individuals and institutions along with the Department of Epidemiologic Research of the Kaiser Permanente Medical Care Program—truly an expansion of the original



*Nothobranchius guentheri* eating mosquito larvae.

composite brain concept. To cite but two salient examples: the connection between the common bacterium *H pylori*, stomach ulcers, and subsequent gastrointestinal cancer, and the link between Epstein-Barr virus (of common mononucleosis notoriety) and Hodgkin's disease with malaria as a co-factor.

This 40th Report presents, with a certain emphasis, OFAS research that has been published in peer-reviewed journals concerning results utilizing the Serum Treasury. Their focus is on prostate, breast, and colorectal cancers. A variety of other published results is reported.

## Insulin & Bio-aging

Although the Serum Treasury has expanded the scope of OFAS research, it has not been a diversion to the original focus on bio-age research. This has proceeded with vigor, most specifically as to how and why dietary restriction of the essential amino acid methionine dramatically reduces bio-aging and, thus, extends and enhances chrono-aging.

As those who read last year's detailed Report\* will know, OFAS has complemented its basic research on bio-aging with investigations into the arena of insulin regulation of glucose metabolism. The insulin metabolic pathway is intimately linked to not only the aging process and its obvious manifestations such as kidney and coronary artery disease, but also in some very fundamental way to lifespan. Therefore, the importance of avoiding the development of insulin resistance, the diminished ability of the body to respond to insulin, cannot be overstated. While an individual's genetic make-up can be a risk factor, there are common sense measures to lessen that risk:

- Limit intake of sucrose and fructose, which can raise triglycerides and link to proteins forming detrimental Advanced Glycation End-products (AGEs)
- Avoid obesity, particularly abdominal obesity, which has very negative effects on insulin activity in the liver
- Exercise regularly to increase insulin sensitivity in muscle tissue
- Follow the Mediterranean diet with its emphasis on unsaturated fats, fish, vegetables, and grains
- Request a Glucose/Insulin Tolerance Test (GITT) by your physician to assess your status and progress
- If diet and exercise are insufficient, there are prescription medications available to improve insulin sensitivity and/or decrease glucose

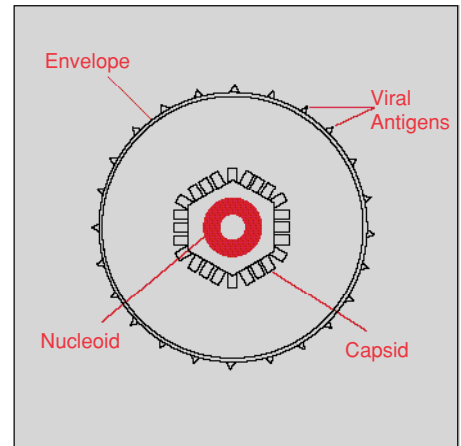
As we enter our 5th decade, OFAS remains dedicated to biomedical research that focuses on developing interventions that prevent, halt, or reverse those disorders that decrease the quality or length of life.



Norman Orentreich, MD, FACP  
Director



David S Orentreich, MD  
Associate Director



The structure of the Epstein-Barr virus is diagrammed. The infectious virus particle consists of 3 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

*With kind permission, from 'The Epstein-Barr Virus,' by Werner Henle, Gertrude Henle and Evelyne T Lennette. Copyright © 1979 by Scientific American, Inc. All rights reserved.*

\* "Glucose/Insulin Metabolism—Emerging Insights", copies of which are available upon request

# Published Results: Prostate Cancer

## Background

*Genetically unusual males who produce little or no dihydrotestosterone develop virtually no prostate cancer and, incidentally, have scant body hair, no scalp hair loss, and do not get acne.*

This is a cancer affecting only males (although women have a vestigial prostate-like organ) and may be male-hormone dependent, although it most frequently occurs at an age when male hormone levels have been in decline for some time. There are many natural chemical variations on the 'classic male hormone' testosterone that circulate in the blood, and it might be one (especially dihydrotestosterone) or more of these (or a balance thereof) that modulate the incidence and progression of this cancer. Note that a small population of genetically unusual males who produce little or no dihydrotestosterone, because they lack the enzyme necessary to convert testosterone to dihydrotestosterone, virtually never develop cancer of their albeit very small prostate and, incidentally, have scant body hair, no scalp hair loss, and do not get acne.

## OFAS Contributions

*Serum levels of key male hormones do not predict likelihood of developing prostate cancer, but intraprostatic levels might.*

Studying serum levels of testosterone and three of its prominent metabolites, OFAS did not find any positive or negative correlation between the likelihood of developing prostate cancer and the serum levels of these various hormones years before the diagnosis. The study does not rule out the possibility that it is the level(s) of one or more of these hormones within the prostate, which can locally transform testosterone into dihydrotestosterone, the male hormone most likely to be the culprit.

**ST** Guess HA, Friedman GD, Sadler MC, Stanczyk FZ, Vogelman JH, Imperato-McGinley J, Lobo RA, Orentreich N.  $5\alpha$ -reductase activity and prostate cancer: A case-control study using stored sera. *Cancer Epidemiol Biomarkers Prev* 1997; 6:21-4.

*Serum levels of Insulin-like Growth Factor-1 (IGF-1) do not predict the likelihood of developing prostate cancer, but unbound levels of this protein hormone might.*

A prominent study by others found that the higher a male's level of IGF-1 was before developing prostate cancer, the higher was his risk. OFAS performed a study smaller but of equal statistical significance and could not corroborate the finding; in fact, OFAS found that the highest incidence of prostate cancer was in the lowest IGF-1 level group. One difference between the two studies that might explain the different findings is that the OFAS study did not measure levels of a relevant IGF binding protein (IGFBP-3); this protein determines the amount of unbound bioactive IGF-1 in serum.

**ST** Schaefer C, Friedman GD, Quesenberry CP (Jr), Orentreich N, Vogelman JH. IGF-1 and prostate cancer. *Science* 1998; 282:199a, 1998. (<http://www.sciencemag.org/cgi/content/full/282/5387/199a>).

# Published Results: Breast Cancer

## Background

Many breast cancer risk factors, known and suspected, are associated with high levels of high-density-lipoprotein cholesterol (HDL-C). Overlapping factors relate to pregnancy rates, socioeconomic status, alcohol consumption, estrogen use, and bodyweight in premenopausal women. Further, studies have shown that HDL-C plays a role in the growth of breast cancer cells in laboratory cell cultures.

On the protective side, a higher level of Vitamin D (whether from diet or sunlight-induced skin production) has been reported; further, there is a report that Vitamin D levels were lower after the diagnosis had been made.

*High HDL-Cholesterol and Vitamin D are recognized beneficials for heart and bone health, respectively. How either relates to breast cancer risk is not clear, but the overall health benefits are clear.*

## OFAS Contributions

Using stored sera from 96 matched pairs of study subjects, OFAS found virtually no difference in the serum levels of the active metabolite of Vitamin D. Indeed, there was no evidence of an increased or decreased trend of risk relative to Vitamin D status at an average of 15 years before the diagnosis of breast cancer. Of course, it is still possible that higher levels of Vitamin D are in some way protective closer to the date of diagnosis.

*Vitamin D levels 15 years before the diagnosis of breast cancer do not portend risk.*

**ST** Hiatt RA, Krieger N, Lobaugh B, Drezner MK, Vogelman JH, Orentreich N. Prediagnostic serum vitamin D and breast cancer. *J Natl Cancer Inst* 1998; 90:461-3.

Studying the stored sera of 200 case-matched controls, OFAS found no significant difference in HDL-C levels on an overall basis. However, those women who were premenopausal at the time of diagnosis had lower levels of HDL-C, and those who were postmenopausal had higher levels than the case-controls. The study's conclusion was that HDL-C might be an independent risk factor.

*HDL-Cholesterol might be an independent risk factor depending on menopausal status.*

**ST** Moorman PG, Hulka BS, Hiatt RA, Krieger N, Newman B, Vogelman JH, Orentreich N. Association between high-density lipoprotein cholesterol and breast cancer varies by menopausal status. *Cancer Epidemiol Biomarkers Prev* 1998; 7:483-8.

# Published Results: Gastrin & Colorectal Cancer

*High serum levels of gastrin are associated with an increased risk of colorectal cancer but only marginally if the relationship is directly causal. Widespread use of new acid-inhibitory medications which induce high gastrin levels might result in increased numbers of cases.*

## Background

This anatomically sited cancer is second only to lung cancer. A diet low in fiber and high in animal protein as well as fat and refined carbohydrates is associated with increased incidence based on broad population studies, but the mechanism(s) is not established. Being a slow-growing cancer, it is typically advanced before symptoms are present. Annual simple testing for blood in the stool is basic and inexpensive. Because the incidence begins to rise at age 40 and peaks between ages 60-75, fiberoptic evaluation of the colon is highly recommended after age 50. Alertness to changes in bowel habits that are persistent or alternating are to be taken seriously.

Gastrin is primarily a stimulator of acid secretion, but it also stimulates growth of the normal surface of colon tissue. The role of gastrin in colorectal cancer is still ambiguous despite extensive studies in animals and human beings.

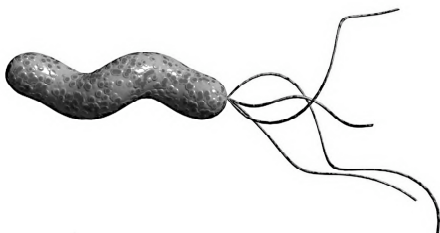
## OFAS Contributions

OFAS participated in a collaborative study involving 250 cases of colorectal cancer and controls matched for age, sex, education, and date of serum collection (mean = 15.3 years prediagnosis). Median gastrin levels were similar in cases and controls; however, an above-normal (>90mg/mL) gastrin level was somewhat associated with this cancer, and an above normal level was statistically associated with 8.6% of all colorectal cancers.

High serum levels of gastrin are associated with low levels of stomach acidity that, in turn, allow for proliferation of microbial flora (such as *H. pylori*) that are normally suppressed by acidity.

The widespread use of new medications (some now over-the-counter and none in use by the subjects in the study) to reduce acidity is an issue; such medications can cause a 2-4-fold increase in serum gastrin. If there is a causal link—even if only in a small percent of the general population—between high serum gastrin and colorectal cancer, the number of persons affected grows substantially.

**ST** Thorburn CM, Friedman GD, Dickinson CJ, Vogelmann JH, Orentreich N, Parsonnet J. Gastrin and colorectal cancer: A prospective study. *Gastroenterology* 1998; 115:275-80.



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



**Hormone supplementation** differs from hormone replacement therapy (HRT) which typically refers to estrogen/progestin replacement for peri- and post-menopausal women. However, hormone supplementation goes beyond this, involving administration (by mouth, injection, or topical application) of hormones that are deemed or suggested to be inappropriately/disadvantageously low. Although HRT has well-established benefits (with certain caveats), the broader concept of hormone supplementation requires clinical caution and careful monitoring pending further and specific scientific evidence.

Orentreich N. Hormone supplementation. *J Geriatric Dermatol* 1997; 5:220-4.

The quest for an ideal material for **soft tissue augmentation** is long-standing. The material's uses would range from treatment of scarring and congenital deformities to the amelioration of the wrinkles and other undesired cutaneous characteristics of aging. The development of an augmenting material derived from a person's own blood is a step forward because it avoids the challenge to the immune system that occurs with non-self-derived biomaterials.

Krajcik R, Orentreich DS, Orentreich N. Plasmagel™: A novel injectable autologous material for soft tissue augmentation. *J Aesthetic Dermatol Cosmetic Surg* 1999; 1:109-15.

The **brain-body response to 'stress'** is mediated by key hormones from the adrenal gland, and these mediate glucose metabolism in a key part of the brain known as the hippocampus. The scientific literature indicates that excessive exposure to such hormones adversely affects memory performance. This collaborative study revealed that although normal elderly persons show appropriately reduced glucose in the brain (and increased serum glucose) in response to the stress hormone cortisol, those with Alzheimer's disease fail to respond. These preliminary findings are intriguingly provocative.

de Leon MJ, McRae T, Rusinek H, Convit A, De Santi S, Tarshish C, Golomb J, Volkow N, Daisley K, Orentreich N, McEwen B. Cortisol reduces hippocampal glucose metabolism in normal elderly, but not in Alzheimer's disease. *J Clin Endocrinol Metab* 1997; 82:3251-9.

On the good side, the **popular dietary supplement chromium picolinate III**, taken in a typical dose to 'regulate' metabolism, does not increase oxidative damage to DNA. Unfortunately, there is also no beneficial effect on glucose or lipid metabolism.

Kato I, Vogelman JH, Dilman V, Karkoszka J, Frenkel K, Durr NP, Orentreich N, Toniolo P. Effect of supplementation with chromium picolinate on antibody titers to 5-hydroxymethyl uracil. *Eur J Epidemiol* 1998; 14:621-6.

Knowing the results of particular **blood androgen metabolite tests** is useful in the diagnosis and treatment of acne and hirsutism in women and of acne and prostate cancer in men. A method has been devised to make these tests simple and direct as well as especially useful when large numbers of samples are to be processed.

Brind J, Borofsky N, Chervinsky K, Vogelman JH, Orentreich N. A simple, differential extraction method for the simultaneous direct radioimmunoassay of androgens and androgen glucuronides in human serum. *Steroids* 1996; 61:429-32.

# New Research Results

Manuscripts in Preparation

## Dietary Methionine Restriction

*Long-term methionine restriction prevents age-related kidney disease and reduces testicular and colon cancers*

Age-related increased vulnerability to chronic diseases is a phenomenon observed in experimental animals and human beings. Fischer 344 rats are particularly susceptible to chronic kidney disease and testicular tumors. Long-term methionine restriction prevents the development of typical kidney disease and significantly reduces the onset and progression of tumors, not only of the testes but also of the colon. Learning how methionine restriction thwarts these diseases inherent in the bio-aging process could have significant impact on our understanding of aging in general.

*Life-long methionine restriction averts the age-related gain of body fat as well as elevated levels of insulin, glucose, and undesirable lipids*

Dietary restriction of the essential amino acid methionine significantly extends the lifespan of laboratory rats. Remarkably, these long-lived rats maintain the metabolic profiles of much younger rats. Methionine restriction averts their normal age-related increases in body fat and blood levels of insulin, glucose, cholesterol, and triglycerides. This suggests that methionine restriction prevents the development of insulin resistance and dyslipidemia with implications for the future treatment of Metabolic Syndrome X in human beings. These findings also support other studies that suggest that insulin-regulated metabolism is intimately linked with the aging process.

*Methionine restriction counteracts the age-related decrease in glutathione, improving cellular defense mechanisms*

Glutathione (GSH) is essential in the cellular line of defense against a variety of toxins. Depletion of GSH is widespread in aging organisms, leading to numerous impairments of function. In collaboration with the American Health Foundation, OFAS previously reported that chronic methionine restriction leads to increases in blood levels of GSH as well as conservation of most tissue levels of GSH during aging. This new collaborative OFAS study extends our earlier findings: it shows that methionine restriction for even as little as 6 weeks causes tissues involved in GSH turn-over to undergo a significant and generally positive change in GSH content. OFAS sees this as an important new model for understanding the impact of nutrition on the bio-aging process.

*Adult-initiated methionine restriction has significant beneficial anti-aging effects*

Benefits from methionine restriction can be gained even if begun in mid-life: adult rats switched from regular laboratory chow to a methionine-restricted chow begin to lose weight even though they are not calorically restricted. Their blood insulin and glucose levels drop along with triglycerides and cholesterol. Most interestingly, maximum lifespan is increased by 15%. Thus, OFAS has shown that an intervention started even after puberty can have a significant impact on classic biological markers of aging and, perhaps, in the fundamental processes of aging itself.

## Insulin & Growth Factors

**ST** Recent epidemiologic studies correlate elevated serum IGF-1 with increased risk of cancer including that of the prostate, breast, and lung. However, most of these studies rely on a single measurement of IGF-1 from one blood sample for each individual. Some, though limited, evidence suggests that blood levels of IGF-1 remain stable for relatively short periods, i.e., months. However, it had not been determined whether a single IGF-1 value reflects an individual's typical level, or longer-term production, of IGF-1. Therefore, OFAS utilized the resources of the Serum Treasury to help define the value of IGF-1 as a biomarker for cancer risk. OFAS demonstrated that participants in this Serum Treasury study maintained a relatively constant level of IGF-1 over a 5-year period, a finding that lends validity to prospective studies that rely on single IGF-1 levels for risk analysis.

Dietary restriction of the essential amino acid methionine significantly extends the lifespan of laboratory rats. Remarkably, these long-lived rats maintain the metabolic profiles of much younger rats. Methionine restriction averts their normal age-related increases in body fat and blood levels of insulin, glucose, cholesterol, and triglycerides. This suggests that methionine restriction prevents the development of insulin resistance and dyslipidemia with implications for the future treatment of Metabolic Syndrome X in human beings. These findings also support other studies that suggest that insulin-regulated metabolism is intimately linked with the aging process.

**ST** The epidemiologic studies showing an increased risk of breast cancer associated with high serum levels of IGF-1 have been mostly clinical or case-controlled studies. These studies cannot differentiate the effects that the presence of tumors have on blood levels of IGF-1 and its binding proteins (BP). Prospective studies avoid this potential source of error. OFAS used the Serum Treasury to analyze levels of IGF and its binding proteins in blood samples drawn at least two years before the diagnosis of breast cancer and compared case and control levels in women who were diagnosed either pre- or postmenopausally. IGF-1 was not associated with an increase in breast cancer risk in either group of women. However, IGF-BP-2 was shown to be protective, particularly against postmenopausal breast cancer. This is the first prospective study to report an inverse association of IGF-BP-2 and breast cancer risk.

Many women experience unexplained diffuse though patterned scalp hair loss. Although many do not have elevated blood levels of androgens sufficient to cause classic androgenetic hair loss, they do have family histories of diabetes and insulin resistance. OFAS looked at the effect of the female hormone estradiol ( $E_2$ ) on metabolism in isolated scalp hair follicles and evaluated the potential interaction of  $E_2$  with insulin and IGF-1. The net effect of  $E_2$  plus IGF-1, a molecule with activity similar to insulin, is an increase in the formation of the very potent androgen dihydrotestosterone. This study indicates that the hyperinsulinemia that occurs in Metabolic Syndrome X might be directly involved in female pattern baldness through an interaction with estrogen in genetically predisposed women.

*Prospective cancer risk studies of Insulin-like Growth Factor 1 (IGF-1) using a single stored serum sample are likely to be valid because its levels remain quite stable over 5 years*

*Life-long methionine restriction averts the age-related gain of body fat as well as elevated levels of insulin, glucose, and undesirable lipids*

*High levels of Insulin-like Growth Factor 1 (IGF-1) are not associated with increased risk of breast cancer, but its type 2 binding protein levels appear to be protective*

*Excess IGF-1 may play a role in some alopecias in females*

# New Research Results: Various

Manuscripts in Preparation

## Hair

*Miniaturized hairs from bald human scalp regenerate and grow normal hairs when grafted to immunocompromised mice, making this an excellent model for evaluating treatments for and understanding the intricate mechanisms of common balding*

Immunocompromised mice provide a unique research tool because they do not reject tissue transplanted from other species. OFAS used these mice to study male pattern baldness. Surprisingly, the atrophic hair follicles of balding scalp, when removed from their natural human milieu, possess a remarkable ability to regenerate and produce hairs equal to those produced by follicles from non-bald scalp. This model might yield not only insight into the mechanism(s) of common baldness but might also be an effective method for screening potential therapies.

*Excess IGF-1 may play a role in some alopecias in females*

Many women experience unexplained diffuse though patterned scalp hair loss. Although many do not have elevated blood levels of androgens sufficient to cause classic androgenetic hair loss, they do have family histories of diabetes and insulin resistance. OFAS looked at the effect of the female hormone estradiol ( $E_2$ ) on metabolism in isolated scalp hair follicles and evaluated the potential interaction of  $E_2$  with insulin and IGF-1. The net effect of  $E_2$  plus IGF-1, a molecule with activity similar to insulin, is an increase in the formation of the very potent androgen dihydrotestosterone. This study indicates that the hyperinsulinemia that occurs in Metabolic Syndrome X might be directly involved in female pattern baldness through an interaction with estrogen in genetically predisposed women.

## Gastric Cancer

*One strain of *Helicobacter pylori*, the bacterium associated with stomach ulcers, induces mutations in a tumor suppressor gene and is possibly associated with more aggressive stomach cancer*

**ST** Infection with *Helicobacter pylori* increases stomach cancer risk. Certain strains of this bacterium produce a protein, CagA, which causes a particularly intense inflammatory response of the stomach lining and are more strongly associated with stomach cancer risk. Genetic disruption of a tumor suppressor gene, known as p53, occurs frequently in various types of human cancers. This collaborative study has shown that tumors from subjects infected with CagA strains of *H. pylori* were significantly more likely to have p53 mutations than tumors from subjects not CagA infected. This might relate to the virulence, type, and location of the stomach cancer.

## DHEAS

*DHEAS protects against angina pectoris and ischemic heart disease in men but not in women*

**ST** Serum dehydroepiandrosterone sulfate (DHEAS) is an abundant adrenal hormone with a poorly understood physiologic role. Men have higher levels than women, but DHEAS declines with age in both sexes. Previous studies found a protective effect of DHEAS against fatal ischemic heart disease. This Serum Treasury study supports that finding and extends the relationship to angina pectoris. The study shows a strong, graded, inverse relation between DHEAS levels and the incidence of angina pectoris in older men. In contrast, high DHEAS levels place women at greater risk of angina and mortality from all causes. Future research will focus on this apparently opposite gender effect of DHEAS on cardiovascular disease.

## Bio-Aging

Effect of life-long calorie or methionine restriction on nutritional markers and gene expression in F344 rats

LifeSpan BioSciences, Inc

Comparison of body composition of methionine-restricted and calorie-restricted F344 rats

Effects of dietary methionine restriction on rat strains other than F344

Effect of methionine restriction on glucose tolerance in F344 and Sprague Dawley rats, as well as changes in glucose tolerance with advancing age

Changes in DNA methylation in tissues of methionine-restricted rats

## Cancer

**ST** Non-Hodgkin's lymphoma in relation to cytokine and growth factor levels

National Cancer Institute

**ST** Association of non-Hodgkin's lymphoma and Epstein-Barr virus with cytokine levels including Insulin-like Growth Factor

National Institutes of Health  
National Cancer Institute

Ultrapheresis for metastatic malignancy

Veterinary Oncology &  
Hematology Research Fund

## Diabetes

Role of hyperinsulinemia and insulin resistance in skin disorders, e.g., granuloma annulare, skin tags, and acanthosis nigricans

Glycation Index of hair as an indicator of diabetes

Effects of sucrose vs dextrose in standard rat chow

## Hair & Sebaceous Glands

Effect of oral or topical administration of 5 $\alpha$ -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, a model for sebum production in acne

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

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

Topical administration of epitestosterone to the flank organ of female Syrian hamsters

Effect of Vascular Endothelial Growth Factor on hair growth

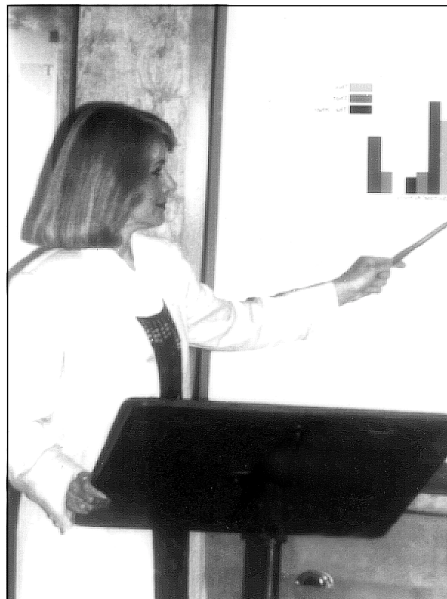
Easton Hospital (PA)

Why implantation of hair follicles from bald scalp into immunocompromised mice produces hair growth

# Seminars

*OFAS holds seminars with a variety of guest lecturers who present their work in fields as diverse as cancer, cosmetic chemistry, nutrition, new technology, epidemiology, and basic biology.*

*Some of the many interesting lectures presented at OFAS over the last five years are noted. Such presentations often lead to long-term collaborations between OFAS and the invited guest and represented institution, which result in the development and exploration of research concepts and the sharing of special resources.*



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

## Insulin

In keeping with our long-standing interest in the growing epidemic of insulin resistance (Metabolic Syndrome X) and diabetes, Dr Walter Futterweit (Mount Sinai School of Medicine, New York, NY) discussed the importance of recognizing and treating insulin resistance in polycystic ovarian disease, a major cause of infertility in young women.

Dr Richard Bernstein, himself a long-time insulin-dependent diabetic, presented practical measures for achieving good blood sugar control.

A promising technology which would spare diabetics painful finger pricks was demonstrated by Ralph Brill Associates (Cold Spring, NY).

## Nutrition & Aging

The role of nutrition in aging and disease, particularly cancer, was presented by Dr John Ritchie (American Health Foundation, Valhalla, NY), our long-term collaborator in methionine restriction studies. He showed that methionine restriction in laboratory rats can either prevent or delay testicular and colon tumors as well as kidney disease.

Dr Leon Ellenbogen (Lederle Laboratories, New City, NY) discussed the vital role of folic acid in methionine metabolism as it relates to the formation of homocysteine, a risk factor in cardiovascular disease. He also reported on the increased risk of colon cancer associated with folic acid deficiency.

Dr H Leon Bradlow (Hackensack University Medical Center, Hackensack, NJ) stressed the importance of adequate dietary indole-3-carbinol (rich sources being vegetables in the cabbage family) because it favorably influences the metabolism of the estrogen estradiol to less carcinogenic forms.

## Hair

Dr Michael Hollick (Boston University School of Medicine, Boston, MA) talked about the unexpected connection between the parathyroid hormone family of peptides and hair growth. Antagonists and agonists of parathyroid hormone-related peptides may one day be used to treat hair growth disorders including the hair loss associated with chemotherapy.

# The Serum Treasury

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 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 both 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  $-40 \pm 2^\circ\text{C}$ .]

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.

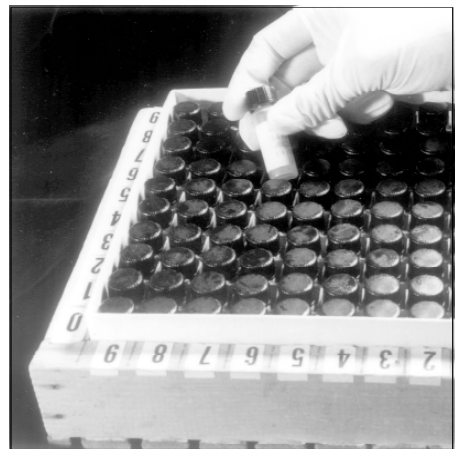
Then came the computer cataloging of each sample so that any given sample could, in fact, be retrieved. Thus was created the Serum Treasury that—with the medical databank already managed by KPMCP—came to be described by the World Health Organization as *“among the most valuable resources currently available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

Since 1984, OFAS has added 119,500 samples from the 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 29 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 of the Serum Treasury, as well as basic information critically pertinent to researchers. Details are available upon relevant request.*

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

### OFAS

Dr RA Krajcik, Assistant Director –  
Scientific Affairs  
Biomedical Research Station  
855 Route 301  
Cold Spring-on-Hudson, NY 10516-9802  
Tel: 845.265.4200  
Fax: 845.265.4210  
E-mail: ofas1@juno.com

# Staff Publications 1961-2001

ST Denotes studies using the Serum Treasury

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# Staff Publications

ST Denotes studies using the Serum Treasury

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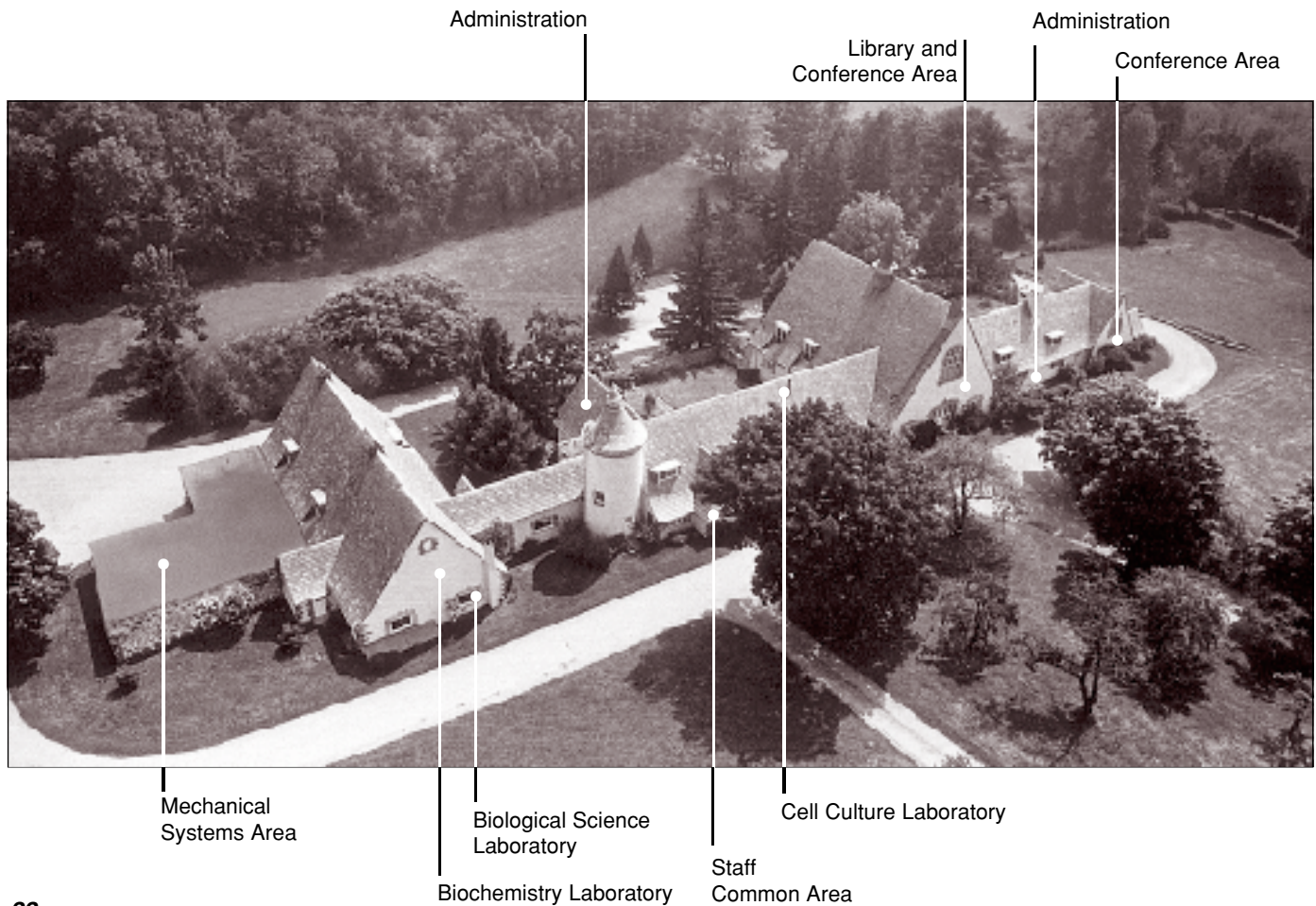
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