Letter from the President
Stephen C. Woods, Ph.D.
Because we are fortunate in having Denny VanderWeele spend a few months with us in Seattle this year, and because our respective labs have both been examining the role of insulin in ingestive behavior for some time, he and I thought it might be instructive to address some points of agreement or lack thereof in our approaches and beliefs about the system. I therefore asked Denny to write a brief statement outlining his approach and where it has led him, and that report begins in the next paragraph. My comments occur at the end of the column.

Insulin and intake - a short summary  
by D.A. VanderWeele
Beginning with a report published in 1980, I have advocated that insulin plays an important role in the production of satiety from ingested foods. This report grew out of some serendipitous findings carried out in streptozocin-induced diabetic animals implanted with osmotic minipumps; as a control condition, I assessed effects of smaller, more modest doses of insulin in normal rats on food intake and body weight. Doses of insulin ranging from 1 to 2U/rat/24 hr reduced spontaneous food intake and at just under 2 U reduced body weight gain over the 7 days of active pumping. In follow-up studies, we found that insulin produced this effect primarily by reducing nocturnal intake, by reducing meal size without affecting meal frequency and without producing frank hypoglycemia.

It is important to integrate the above findings with our streptozocin work. In animals given diabetes-producing doses of streptozocin, rats demonstrate the advent of the disease, in our studies, by initially increasing meal size. Only after significant weight loss occurs does an increase in the number of meals also appear (VanderWeele & Gorang, 1983). Another report also noted that in insulin-normal rats, subdiaphragmatic truncal vagotomy attenuated the suppression produced by the minipump-administered insulin and an attenuation was also produced in animals induced to become obese by a modified "variety" diet (Vanderweele, Haraczkiewicz & Van Itallie, 1982).

Dr. Rhonda Oetting-Deems and I then proceeded to examine the effects of insulin
administration on sham feeding, a technique others had used to argue for satiety status for other hormones. We demonstrated clearly that insulin administered in acute doses to insulin-normal animals of 0.4 or 0.8 U/rat reduced sham feeding. The animals were not suffering from hypoglycemia-induced malaise, as they preferred the flavor(s) of milk paired with insulin injections over those paired with saline injections in the sham-feeding studies. We were pleased to note the reports of Giza & Scott and colleagues as they showed that glucose infusions or insulin injections were capable of reducing afferent discharges to sweet tastes placed on the tongue; thus, insulin may work, in part, to reduce the sensory reward qualities of ingested nutrients (similar to the seminal, historic predictions of drive and drive reduction theory.)

I next proceeded to assess the "physiologic" possibilities of our early minipump studies. The first studies clearly raised levels of circulating insulin outside the physiologic range, despite our use of doses considerably below those already used in published studies. As Shimazu (1967) had shown that insulin could modulate glycogenic enzymes in the liver, I implanted a catheter into a mesenteric vein (of the rat) and threaded the catheter into the hepatic-portal vein. Rats were trained to bar press for food, and 10 pellets into each spontaneously occurring meal they were infused with 1 or 2 mU of insulin intraportally. Meals in which insulin administration took place were reduced in size from 5.3 to 89.1%. All animals tested to date have shown reliable reductions to insulin at these two doses; however, insulin at the same dose administered into the jugular vein does not cause a reliable decrease in meal size.

We felt that exogenously administered insulin, even at the lowest doses we had tested, could not settle the endogenous issue; that is, can release of pancreatic insulin in the spontaneously eating rat be shown to enhance satiety. On the surface, insulin release correlates with the ingestion and absorption of foods and inhibition of insulin function in diabetes produces considerable enhancement of hunger. Can the inducement of normal insulin release to eating enhance satiety? With Dr. Joseph Vasell and Edward Haraczkiwicz, I have recently shown that injections of tolbutamide just prior to a well-signalled meal reduced spontaneous food intake. Tolbutamide was shown to enhance insulin release and produce enhanced glucose clearance in animals not allowed to eat on the same schedule. Phentolamine produced similar effects (peripheral alpha-adrenergic blockade enhances insulin release to food ingestion) in mildly deprived and refed rats. Thus, it appears that enhancing insulin release to normal food ingestion can reduce intake; the insulin does not require outside, exogenous hormone to produce satiability.

Finally, with Drs. Rhonda Deems and Robin Kanarek, I have recently shown that exogenous insulin can speed stomach emptying of a milk-type diet. This role of insulin may also
contribute to the shortening of the spontaneously occurring meal as nutrients can contact gastrointestinal receptors more rapidly, enter the blood stream and clear from the circulating energy pool. While this may produce aversion through malaise in liquid diets, it is doubtful that emptying of solid foods would be affected to the same degree.

Thus, the evidence for insulin as a short-term signal participating in the sequence of stimuli arising from the spontaneous meal resulting in the production of satiety is multiple. Exogenous insulin reduces meal size without affecting meal frequency; renders gustatory afferents less sensitive; enhances the clearance of glucose from the plasma, and accelerates stomach emptying, at least for liquid diets. With insulin deficiency, continuous and increased hunger results and is associated with increased meal size (and, if weight loss occurs, increased meal frequency). Insulin elicits these effects without producing signs of illness; indeed, sham-feeding rats preferred flavors paired with insulin over those paired with saline injections. I feel that insulin contributes to satiety by increasing the rate and efficiency of clearance of glucose from absorption and the circulating energy pool (a concept of Brobeck, 1975), and particularly at the site of the liver by modulating glycogenolytic enzymes (to favor glycogenesis). Additionally, insulin dampens sweet hedonics.

This hypothesized role for insulin in aiding the production of satiety from feeding can also be viewed as consistent with the longer-term effects posited by some. By increasing the efficiency of glucose uptake from meals, insulin might contribute to the correlation between the calories from a meal (at least CHO calories) and the length of the intermeal interval. As most animals do not postpone initiation of meals until insulin is no longer producing glucose utilization, insulin can still contribute to the induction of food intake by producing the hypoglycemic episode some cite as indicative of the onset of a meal (DAVW).

Insulin and intake - a reply by S. Woods

For many years, Dan Porte and myself (and numerous excellent colleagues) have pursued implications of the hypothesis that if insulin provides a signal directly to the brain that influences feeding behavior. Since pancreatic insulin secretion is directly related to adiposity, we feel that this system allows integration of body fat stores into the complex calculus that controls meal size, and thereby helps maintain or stabilize adiposity across a variety of situations and conditions. Historically, we believed that the presence of insulin within the cerebrospinal fluid (CSF) provided a valuable key in the understanding of the system. When we increased plasma insulin, the consequent increase of CSF insulin was delayed by over an hour; and when we infused exogenous insulin directly into the CSF of animals, a clear reduction of food intake was not apparent in the next meal. We felt that
whereas insulin unambiguously reduced food intake and body weight, it was probably a long-term signal that was unlikely to work on a meal-to-meal basis (at least when it acts via the CNS). However, since eating by most animals necessarily involves meals, the insulin-adiposity system had to interact with individual meals at some level. Our finding that small, subthreshold doses of insulin slowly infused into the CSF of both rats and baboons, while having no obvious effect of its own, enhanced the efficacy of peripherally administered CCK at reducing meal size suggested that insulin may act to modify other regulators of meal size. Thus, changes of adiposity could be manifest within the CNS as subtle insulin-induced changes in the gain of other "satiety" signals.

It should be clear that such a hypothesis could be quite independent of the system described so elegantly by VanderWeele above. He has compelling evidence that insulin works in the periphery to contribute to satiety. This makes a kind of teleologic sense in that it seems appropriate and parsimonious that the same hormone, being secreted in proportion to what is being eaten as well as to the degree of fat stores, should work in more than one way (and site) to achieve the same end. I believe that in Denny's more chronic experiments, in which non-hypoglycemic doses of insulin are slowly infused peripherally, some of the infused insulin reaches the CNS and contributes to the reduced eating and loss of body weight; but there are probably peripheral effects as well. Similarly, I am not that certain that the brain-insulin system need take as long to become activated as I once thought. Recent evidence from several labs (including that of Michael Schwartz in our group in Seattle) suggest that the most likely route of entry of insulin from blood to brain is via the brain capillary endothelial walls (where it appears to be transported into the brain in intact form), and not the choroid plexus-to-CSF-to-brain route as we previously thought. This means that circulating insulin might have much closer and faster access to critical brain sites. Putting exogenous insulin directly into the CSF and looking for behavioral changes may be going against the natural flow of the system. Changes of feeding certainly occur, but only after a lag of one or more days. Further, more recent data gathered by Anton Steffens and Jan Strubbe when they spent time in my lab suggest that when plasma insulin is increased in awake rats, the change of insulin levels that can be observed in the CSF occurs within minutes. The point is that I am not ready to rule out the possibility that insulin might, in fact, gain sufficiently rapid access to the brain to act within the time frame of an ongoing meal. The other point, of course, is that I view (and I think Denny concurs) our work as being in agreement with that of VanderWeele. (SCW)
Position openings

H. Weingarten wrote recently that there are several vacant positions (post-docs, assistant profs) in the Psychology Department at McMaster University. For more details, write to Harvey Weingarten, Psychology Department, McMaster University, Hamilton, Ontario, Canada L8S 4K1

Human Eating Behavior

Position available at the Johns Hopkins University School of Medicine. Candidate for position should preferably have postgraduate degree (Ph.D.), but others will be considered. Should have knowledge of nutrition, dietetics, physiology, psychology or related field. Statistical background, data entry and analysis desirable; project management and administrative skills involved. Send curriculum vitae and three letters of reference to: Dr. Barbara Rolls, Meyer 207, Johns Hopkins School of Medicine, 600 N. Wolfe St., Baltimore, MD. 21205. Equal Opportunity/ Affirmative Action Employer.

Finally, Gerard Smith wrote recently that the Bourne Laboratory has two postdoctoral research training fellowships in the normal and abnormal controls of eating. The fellowships are usually awarded for two years and the stipends are competitive. Letters of interest and C.V.’s should be sent to: Gerard P. Smith, M.D. E.W. Bourne Behavioral Research Laboratory, New York Hospital-Cornell Medical Center, Westchester Division, 21 Bloomingdale Road, White Plains, NY 10605.

The Philosopher's Corner
by Harry R. Kissileff

DIVERSITY—Part II

I have been trying to design some experiments to determine the origin of binge eating in bulimia. The problem that has come up however is relevant to many of the experiments in our field. Since I am unsure about the solution of this problem, I am asking for help from you. Here is the problem:

I would like to design an experiment to test the hypothesis that factor X is involved in phenomenon Y. You can fill in the factors being manipulated with anything from stimulation of the hypothalamus to nutrient consumption or selection, to neurotransmitters or cognitive factors like anxiety or depression. In my case, I am interested in determining whether the absence of satiety (X) is a cause of binge eating (Y). A classic approach to this problem is if X causes Y then if I remove X (or put it back if a lack of it causes Y), Y should disappear (or reappear). In my case if I put back satiety in some way, and binge eating disappears, have I proved the point? Why should that be so? In fact it will only be so if X is the only cause of Y. Even then the removal of X and disappearance of Y does not establish cause and effect. Why not? First it must be recognized that there is only one valid way to verify such a conditional. One must show that when X is present Y is also, under all conditions and
at all times. Since it is impossible to do this, confidence is built up statistically by calculating the percentage of successful trials of such a conditional. Removal or denial of X simply makes the conditional indeterminate. Although Quine (Mathematical Logic, Harvard U. Press, 1961, p. 14-15) states that all truth-functional conditionals with false antecedents (i.e. denials of X) are true, he is also ambivalent about this conclusion, and implies that the conditional states nothing about the consequent when the antecedent is false. Ingestive behavior has been through this problem in the case of brain function study by lesion and other extirpation experiments. In limited situations such an approach may sometimes be applicable, such as at the inception of an investigation, when one is looking for a path. Most of classical endocrinology and neuroscience was built on this model. However, as a general rule, it is not valid.

The alternative approach of corroboration by nullifying a prediction from the conditional is equally indeterminate, though frequently touted. In this case the consequent is denied and thereby the hypothesis (antecedent) is disproved. In other words if X predicts Y and Y does not occur X is disproved. I dealt with this fallacy in a previous column (SSIBling's I (3), Kuhn's 4th point).

The conclusion is that since it appears to be futile to set up experiments to test even simple hypotheses, it would be even more futile to test multiple or complex hypotheses. What then is the alternative? There are two alternatives: One is that I have completely misunderstood the logic of scientific experimentation, which is possible. If that is true, I'm in good company. Most of us at one time or another have tried to set up experiments to test hypotheses. In that case, I hope someone will correct me, and I will publish the retraction in the next issue! One possible way out of this dilemma, of rejecting so much of what has been considered the backbone of modern science is to acknowledge that scientific knowledge progresses in stages. What is appropriate at one stage may be inappropriate later.

The other possibility is that I am correct, in which case there are probably many alternatives. One of the simplest however is to substitute the logic of testing hypotheses for the logic of testing what David Booth has referred to as testing mechanisms, by which he means measuring the shapes and magnitudes of input-output relationships in biological systems. Many experiments in fact do just that. Any dose-response relation is such an experiment. It does not test the truth or falsity of a down to earth example, gravity is not a factor or hypothesis about whether objects fall. It is the constant that expresses the relationship between the speed an object acquires, or the distance it moves during a free fall, and the duration of its fall for particular period of time.

Can the same be said about
factors which we study in ingestive behavior, sensory qualities, CCK, stomach distention, hypothalamic activity, reinforcing value? Should these be studied as hypotheses (X causes something) to be verified or falsified, or necessary and sufficient conditions for ingestive behavior or as partners in input-output relationships with measures of ingestive behavior? Alternatively, if one wants to hedge the bet, when is each one appropriate? Readers may appreciate the additional discussion of this issue which is laid out very instructively in a little book by W. Bechtel "Philosophy of Science - an Overview of Cognitive Science" (Erlbaum Associates: Hillsdale, NJ, 1988). Is this information useful, superfluous, or wrong? Please direct your answers to Dr. Kissileff.

**PERSONAL**

JCS - I checked....there isn't any walnut used in making the paper. - TWC

**On Abbreviations**

It has been brought to my attention that several of our readers have become very amused/upset with the use of some of the acronyms that have appeared in this newsletter. To remedy this oversight, below is a list of the more commonly used abbreviations that you, the devoted reader, might find in this or other issues of SSIBlings. New acronyms will be added to this list from time to time. Please drop me a note if you have others that you wish published. Please note that *your* name will also be included as the submitting proponent of the acronym's inclusion in the list! - TWC

**EPA**

Eastern Psychological Association

**NAASO**

North American Association for the Study of Obesity

**FASEB**

Federation of American Societies for Experimental Biology

**SSIB**

Society for the Study of Ingestive Behavior

**IBRO**

International Brain Research Organization

**SN**

Society for Neuroscience

**Calendar of Events**

**Oct 24**

Deadline for Eastern Psychological Association (EPA) abstract

**Oct 29 - Nov 3**

Annual meeting of the Society for Neuroscience. Phoenix, AZ

**Nov 2**

*Physiological Psychology: The Control of Ingestion by Peptides.* (see below)

**March 31 - April 1**

EPA Annual Meeting, Philadelphia, PA

Annual Meeting

This year, SSIB is sponsoring a special seminar at the annual Neuroscience meeting. The seminar will be chaired by S.C. Woods and is entitled: *Physiological Psychology: The Control of Ingestion by Peptides.* Included in the roster of speakers is: P. Geiselman (*Introductory Remarks*), J. Gibbs (*Peptides and the Control of Food Intake*),
On the question of whether we should meet jointly with the North American Association for the Study of Obesity (NAASO), there were 80 in favor, 17 opposed and 14 undecided or no answer. However, the number who said they would actually attend was lower (70); 25 said they would not attend; and undecided remained at 14.

**Plan Now for Spring Meeting**

The Society will again be meeting with the Eastern Psychological Association (EPA), March 29 – April 1, 1990, in Philadelphia. Those members who are not members of EPA can obtain a call for papers, if they wish to include more than the SSIB 5 minute talk from Dr. Murray Benimoff, EPA Executive Director, Dept. of Psychology, Glassboro State College, Glassboro, NJ 08028. Everyone should be sure to check the INGESTION category and indicate it in the proper abstract blank location, if he or she wishes the submission to be reviewed by an EPA program committee member who is familiar with ingestive behavior.

Harry R. Kissileff, Executive Officer

**Clip 'N Save**

**New addresses**

For those of you who like to keep track with this sort of thing, below you will find several additions and changes to the SSIB directory. Suggestion: Cut this section out and tape it into your SSIB Directory for future reference.
E-mail addresses and FAX #'s

Bartoshuk, L.  
Bernstein, I.L.  
Blackburn, J.R.  
Capaldi, E.D.  
Hoebel, B.G.  
Houpt, T.A.  
Kennitz, J.W.  
Murphy, R.B.  
Novin, D.  
Parham, E.S.  
Steffans, A.B.  
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HOEBELO@PUCC  
HOUPTA@MUSCB.BITNET  
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Address changes

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Dr. Simon N. Thornton  
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11, place Marcelin Berthelot  
75231 Paris Cedex 05  
France

Mark your Calendars

The International Life Sciences Institute-Nutrition Foundation will be sponsoring an international conference on "Thirst: Physiological and Psychological Aspects" that will be held May 9-11, 1990 at the Ramada Renaissance Hotel in Washington, D.C. For further information about the meeting, please contact Ms. Lili Merritt, conference Coordinator, International Life Sciences Institute, 1126 Sixteenth St. N.W., Washington, D.C. 20036

Comings and Goings

Several members of the society have recently changed addresses. B.G. Stanley is no longer found in New York City. Rather, he has moved to the University of California - Riverside, where he assumes the job of Assistant Professor of Psychology.

Another member that has just recently moved is Barbara J. Moore, who has left Rutgers University to take a job as Director of International Programs at Weight Watchers International. Barbara will be developing weight loss regimens that are in tune with the cuisines and food habits of people from various ethnic and cultural backgrounds.

Harry Carlisle has finally returned to the University of California - Santa Barbara from a sabbatical leave in the UK, where he was reportedly working with Michael Stock. It seems that Mike has now joined Harry in Santa Barbara for his sabbatical.

1989 SSIB Election Results

President-Elect: Alan N. Epstein, M.D.  
Secretary: Bartley G. Hoebel, Ph.D.  
Treasurer: Anthony Sclafani, Ph.D.

Board of Directors:  
Donald V. Coscina, Ph.D.  
Henry Koopmans, Ph.D.  
John D. Davis, Ph.D.

1989 Annual SSIB Business Meeting

The Annual Business meeting will be held during the SSIB Social at the Neuroscience Meeting, 5:30 - 7:30 P.M., Thursday, November 2, 1989, in Phoenix Arizona.