
The Center for Plants and Human Health: An Interdisciplinary Approach

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The Center for Plants and Human Health is a new interdisciplinary initiative that will serve to stimulate collaboration among scientists at the University of Minnesota who are interested in how plants and plant products may be used to improve human health and nutrition.

In recent years a great deal of attention has been drawn to the potential for plants and plant products to contribute to human health. This interest goes under a wide variety of labels—phytonutrients, nutraceuticals, functional foods, complementary and alternative medicine, *etc.*—and encompasses plant science, natural-products chemistry, pharmacology, nutrition, and laboratory and clinical medicine. It includes the development of raw produce and processed foods that are effective in prevention and treatment of disease, as well as identification of naturally occurring plant products that may have preventative and curative properties when used in a purified form. It also includes the testing of these foods and compounds for efficacy and toxicity in humans and animals. The University of Minnesota Twin Cities campus is one of the few major research universities in the country that has both an academic health center and a college of agriculture. We have a large number of faculty members who have active programs in this area, but we have had no formal mechanism to bring them together to develop interdisciplinary research programs directed toward the interface between agriculture and medicine.

The Center provides a forum for the development and interchange of information relevant to plants and human health and serves as a stimulus for interdisciplinary collaboration leading to new research opportunities and funding in this vital area. The Center for Plants and Human Health complements and collaborates with previously existing groups such as the Center for Spirituality and Healing and the Center for Addiction and Alternative Medicine Research to stimulate interaction among scientists and clinicians at the University of Minnesota.

CENTER STRUCTURE

The Center for Plants and Human Health is funded as an Initiative in Interdisciplinary Research, Scholarly, and Creative Activities by the Office of the Vice-President for Research of the University of Minnesota, with additional support from the Deans of the Medical School and the College of Agricultural, Food, and Environmental Sciences (COAFES). The Center is governed primarily by a Steering Committee of six faculty members representing the health sciences and agriculture. Current members are:

- Jerry Cohen, Bailey Professor of Environmental Horticulture, Horticultural Science,
- Vincent Fritz, Professor, Horticultural Science and Southern Research and Outreach Center,
- Stephen Hecht, Wallin Professor of Cancer Prevention, Cancer Center,
- Greg Plotnikoff, Medical Director, Center for Spirituality and Healing,
- Joseph Warthesen, Professor and Head, Food Science and Nutrition,
- Gary Gardner, Professor, Horticultural Science.

I serve also as Director of the Center, the day-to-day activities of which are managed by Program Coordinator Karen Kaehler.

CENTER PROGRAMS

The study of plants and human health can be approached from many directions. At the Center we are examining the interface of agriculture, defined as the art and science of purposeful breeding, cultivation, and harvesting of plants for human use, and of medicine, defined as the art and science of purposeful action to maintain human health. To assist us in developing opportunities for collaboration between COAFES and the schools of the Academic Health Center, we created a map of this interface (Figure 1). Grouped around the general themes of Production and Consumption are specific activities or topics, such as Cultivation, Disease, or Culture. From there, colleges and departments, such as Horticultural Science, or Public Health, were identified. This endeavor has brought together over a hundred researchers from sixteen colleges, departments, and institutes within the University of Minnesota.

The Center is not contained within a building, neither is it an academic department. It is a virtual organization that exists to be a matchmaker by bringing scientists together. Our focus is on research on plants and plant products, broadly defined. Our programs fall into three general categories:

- Interdisciplinary Forum on Plants and Human Health, with monthly meetings of scientists and practitioners from throughout the Twin Cities campus and community. Thus far, the Forum has focused on three activities:

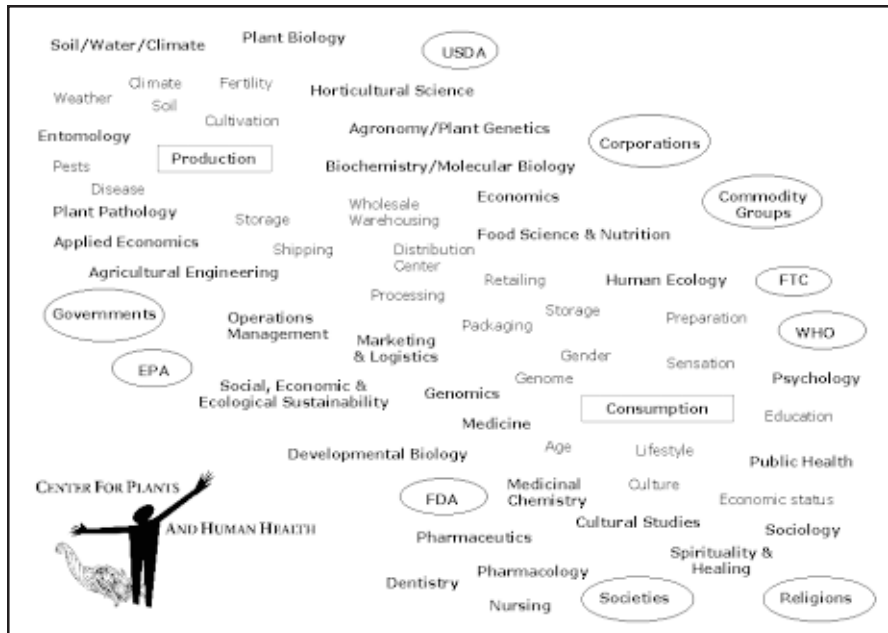


Figure 1. Map of the interface between medicine and agriculture.

- colloquia featuring local researchers to gain detailed understanding of the work in progress in Minnesota as a basis for collaboration;
- a symposium featuring leading national experts in this area, both from agricultural and medical perspectives, to achieve a common understanding of the state of the science in this field; and
- focused discussion groups on topics of broad interest within the university, to determine if there is a specific basis for formal research collaboration. Thus far, discussion groups have been held on topics such as vegetables and chemoprevention, soy products and human health, botanicals, and whole grains.
- Travel Funds for Interdisciplinary Meetings and Collaborations. In addition to bringing external scientists to campus, the Center provides funds to allow University of Minnesota faculty, students, and staff to attend scientific conferences on this topic that they would not otherwise be able to attend. We also provide funds for University of Minnesota personnel to visit scientists at other institutions who are potential collaborators.
- Grant Writing and Coordination. In putting together large, interdisciplinary grant proposals, there is often a lack of time and skilled personnel to write, assemble, and coordinate complex documents across departmental and collegiate boundaries. Major functions of the Center are to identify

realistic opportunities for funding of interdisciplinary research related to plants and human health (hence the focused discussion groups mentioned above), to assist the Principal Investigators in writing such proposals, and to coordinate the bureaucratic details that are required to submit them.

ONGOING RESEARCH RELATED TO THE MISSION OF THE CENTER

Although the Center is new, many examples of current research at the University of Minnesota fall within its scope, a few of which are described below.

Propolis and HIV Infection Propolis is a resinous substance collected by honeybees from certain species of trees and shrubs. It is used to seal the hive and has thus been called “bee glue,” although “bee caulk” may be more appropriate. It is a complex mixture of over 180 compounds, including flavonoids, caffeic acid, prenylated *p*-coumaric acids, and acetophenone derivatives. Propolis has been used as a natural biocide, literally, for centuries; a large database supports *in-vitro* antimicrobial activity of propolis against a variety of pathogens; and it has been shown to have broad anti-inflammatory and analgesic properties as well.

Philip Peterson of the University of Minnesota Medical School and the Hennepin County Medical Center and his colleague Genya Gekker have been evaluating the effects of propolis on HIV expression in CD4+ lymphocytes and microglia. In preliminary experiments they find that propolis has antiviral activity against HIV-1 variants in both cell types and that it does not antagonize the anti-HIV activity of standard antiretroviral drugs such as zidovudine (AZT) or indinavir. Propolis may have an additive effect on AZT activity (P.K. Peterson, personal communication). Currently, experiments are being planned with collaborators in clinical medicine and pharmacy to determine the clinical efficacy of propolis against HIV and with scientists in entomology and horticultural science to determine the biological and chemical nature of the active components.

Effects of Soy Consumption on Blood Lipids Since Minnesota is a leading soybean-producing state, it is not surprising that there is a great deal of interest in the beneficial aspects of soy consumption, both for chemoprevention of cancer and for cardiovascular health. One such example of on-going research comes from the laboratory of Mindy Kurzer in the Department of Food Science and Nutrition. Dr. Kurzer and her colleagues (Wangen *et al.*, 2001) carried out a randomized crossover trial of eighteen post-menopausal women who consumed three different isolated soy proteins for 93 days. These treatments provided three levels of isoflavones: 7 (control), 65 (low), or 132 (high) mg/day. Plasma LDL cholesterol was significantly lower during the high-isoflavone diet (Figure 2A), and the ratio of LDL:HDL cholesterol was significantly lower during the high- and low-isoflavone diets than during the control diet (Figure 2B).

Isoflavone consumption did not significantly affect total cholesterol, HDL cholesterol, or the total cholesterol:HDL ratio. Although these effects were small, it is possible that isoflavones would contribute to lowering the risk of cardiovascular disease if consumed over many years in conjunction with other lipid-lowering strategies.

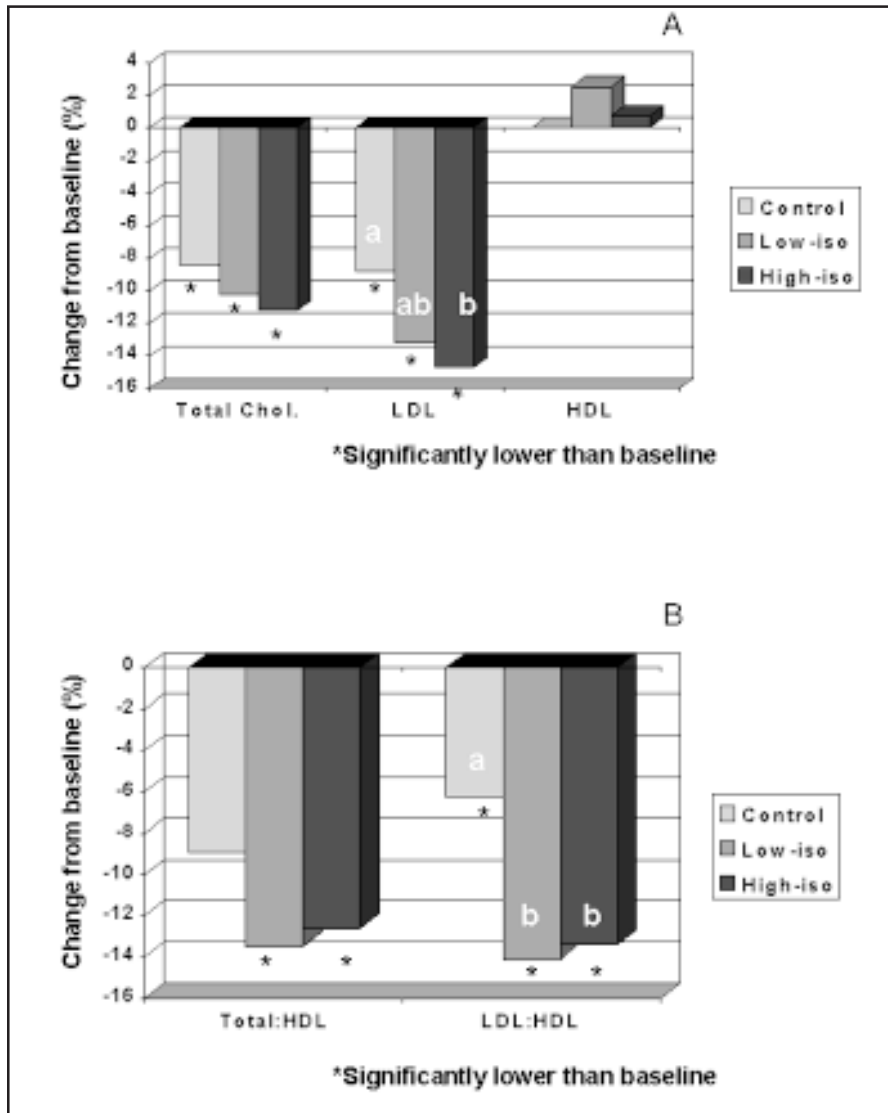


Figure 2. Effects of soy on cholesterol and lipids in post-menopausal women (adapted from Wangen *et al.*, 2001).

The breadth of research on soybean at the University of Minnesota offers significant interdisciplinary synergy. For example, the potential for collaboration between scientists in Nutrition and the Academic Health Center and those in Agronomy and Plant Genetics in the areas of soybean breeding and soybean molecular biology could lead to more-precise identification of the components of soybean that are responsible for beneficial effects on human health.

Isothiocyanates for Chemoprevention of Lung Cancer The University of Minnesota has a long history of research on the relationship between vegetable consumption and chemoprevention of cancer, largely due to the pioneering work of Lee Wattenberg of the Department of Laboratory Medicine and Pathology (e.g., Wattenberg, 1977). This tradition is being continued in the laboratory of Stephen Hecht in the University of Minnesota Cancer Center.

Consistently, studies demonstrate that vegetable consumption, including cruciferous vegetables, is protective against lung and other forms of cancer. These observations led to the hypothesis that there are chemopreventative agents in vegetables. A likely candidate for this activity is a class of isothiocyanates. These compounds exist in cruciferous vegetables as their glucosinolate conjugates, and when these vegetables are chewed or otherwise macerated, the plant enzyme myrosinase catalyzes the hydrolysis of the parent glucosinolate, releasing the isothiocyanate. There is considerable evidence in the literature that isothiocyanates have chemopreventative activity in animal models (Hecht, 2000).

One example of the chemopreventative effect of isothiocyanates comes from Dr. Hecht's laboratory. Phenethyl isothiocyanate (PEITC) occurs as its glucosinolate conjugate, gluconasturtiin, in a variety of cruciferous vegetables, including watercress, turnip, Chinese cabbage, and cabbage. Dietary PEITC was tested as an inhibitor of lung tumorigenesis induced in rats by the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (Hecht *et al.*, 1996). In the rats with NNK (2 ppm in the drinking water), 70% had adenoma or adenocarcinoma of the lung (Table 1). In the rats treated with PEITC (489 ppm in the diet) and NNK, complete inhibition of lung tumorigenesis was observed. PEITC alone had no significant tumorigenic or toxic activity.

Regulation of the Chemopreventive Constituents of Vegetables in the Diet The work of Drs. Hecht and Wattenberg, as well as many other reports of the chemopreventative properties of isothiocyanates, has led to a fourth example of work related to the mission of the Center for Plants and Human Health. This project is funded by the SOTA TEC Fund of the Blandin Foundation, and it developed in parallel to the Center although it exemplifies the kind of broad, interdisciplinary work that we seek to foster.

The overall goal of this project is to maximize the concentration of cancer

TABLE 1. LUNG TUMOR INDUCTION IN RATS TREATED WITH NNK OR NNK PLUS PEITC (ADAPTED FROM HECHT ET AL., 1996)

Treatment	Number of rats	Rats with lung tumors(%)
NNK	56	39 (70)
NNK + PEITC	59	3 (5)
PEITC	19	2 (11)
None	18	1 (6)

chemopreventative agents in vegetables, *i.e.* in the diet rather than as a supplement. The project has focused on glucosinolates, because of the results discussed above, and has three objectives:

- whole-plant studies to determine the environmental conditions that influence the biosynthesis of these compounds;
- applied (field) studies to optimize the content of these compounds in harvested plant material; and
- applied studies to determine the effects of various postharvest and processing treatments on the content of these compounds in vegetables in the diet.

The organization of this project is complex. There are ten co-principal investigators in four departments: myself, A. H. Markhart, and John Erwin of the Department of Horticultural Science directing growth chamber experiments; Vince Fritz of the Southern Research and Outreach Center and Horticultural Science, and Carl Rosen of the Departments of Horticultural Science and Soil, Water, and Climate directing field studies; Jerry Cohen of the Department of Horticultural Science and Steve Hecht of the Cancer Center directing the chemical analyses; Cindy Tong of the Department of Horticultural Science directing postharvest studies; Bill Schafer of the Department of Food Science and Nutrition directing the processing studies; and Dan Gallaher of the Department of Food Science and Nutrition carrying out animal feeding studies to evaluate the chemopreventative properties of the produce in diet.

This work is in progress, and I have three examples of preliminary data from our controlled environment studies. The first is from A.H. Markhart and Lynette Wong who are examining the effects of water stress on the gluconasturtiin content of watercress. Ms. Wong stressed watercress plants by withholding water until there was visible wilting in the youngest leaves. At that time, tissue was either harvested (one stress cycle) or plants were re-watered daily for three days. In separate experiments, plants were subjected to a second water-withholding treatment followed by re-watering. These results are shown in Figure 3. After two cycles of water stress, plants showed a highly

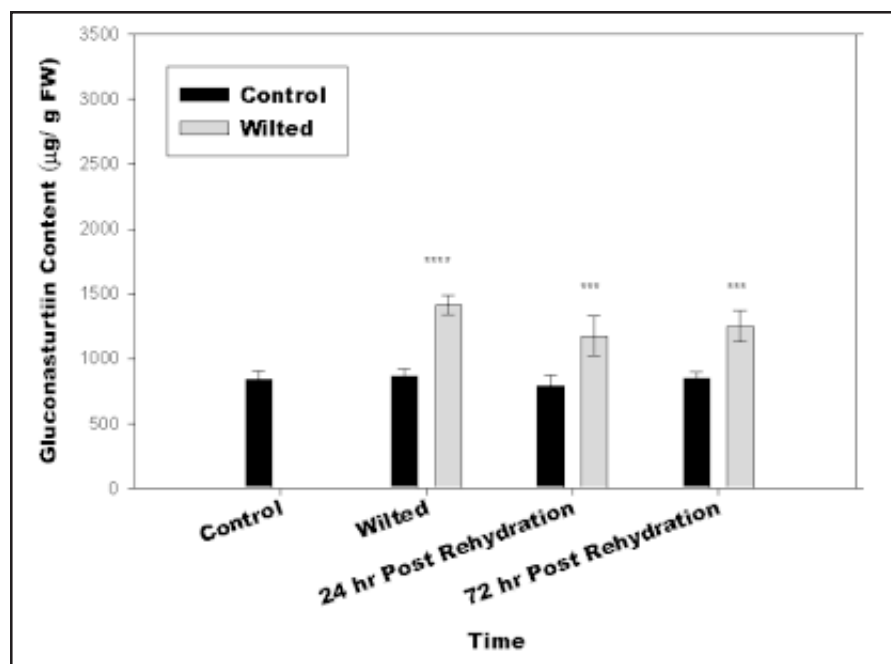


Figure 3. Two cycles of water stress on mean fresh weight gluconasturtiin content in watercress (** $P \leq 0.025$, **** $P \leq 0.001$).

significant increase in gluconasturtiin content (on a fresh-weight basis). After 24 and 72 hours of re-watering, stressed plants had lower gluconasturtiin levels than the wilted plants (not re-watered); however, levels were still significantly greater than in plants that had never been stressed.

Two other examples of preliminary data from our controlled-environment experiments come from the work of Gerard Engelen-Eigles in my laboratory. Figure 4 demonstrates a temperature effect on gluconasturtiin content. Plants grown under a 20°C day/16°C night regime had a higher gluconasturtiin content on a fresh weight basis than those grown under a constant 20°C, and this difference increased over time. Therefore, cooler night temperatures seem to favor glucosinolate production. We are also examining various aspects of the effects of light on the gluconasturtiin content of watercress. One example is shown in Figure 5. Plants grown under metal-halide lamps (white light) showed an increase in gluconasturtiin with red-light supplementation from fluorescent lamps. This increase did not occur if the metal-halide light was enriched with far-red light. Our studies are continuing to further define environmental conditions in the laboratory and field that influence the biosynthesis of these compounds.

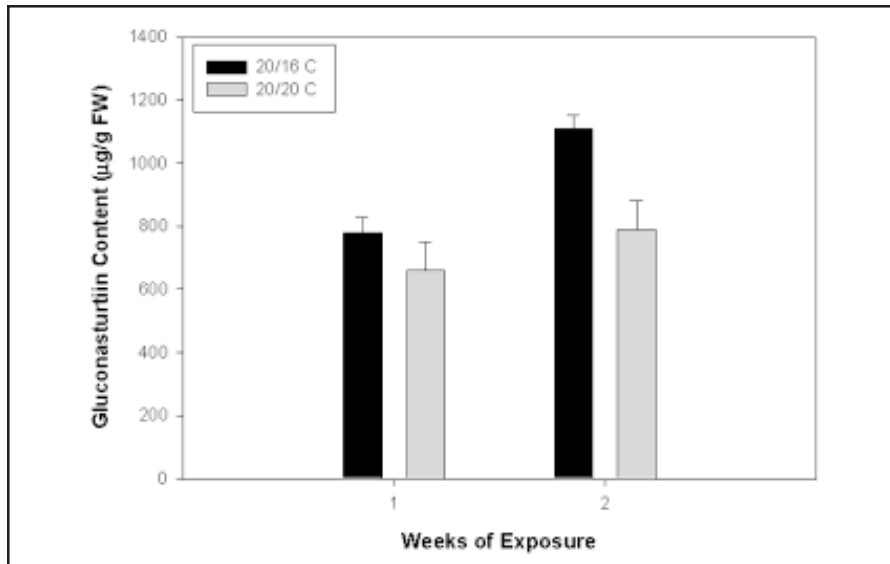


Figure 4. Effect of day and night temperatures on gluconasturtiin content in watercress. [photosynthetically active radiation (PAR): 450 $\mu\text{mol}/\text{m}^2/\text{s}$ from metal halide lamps]

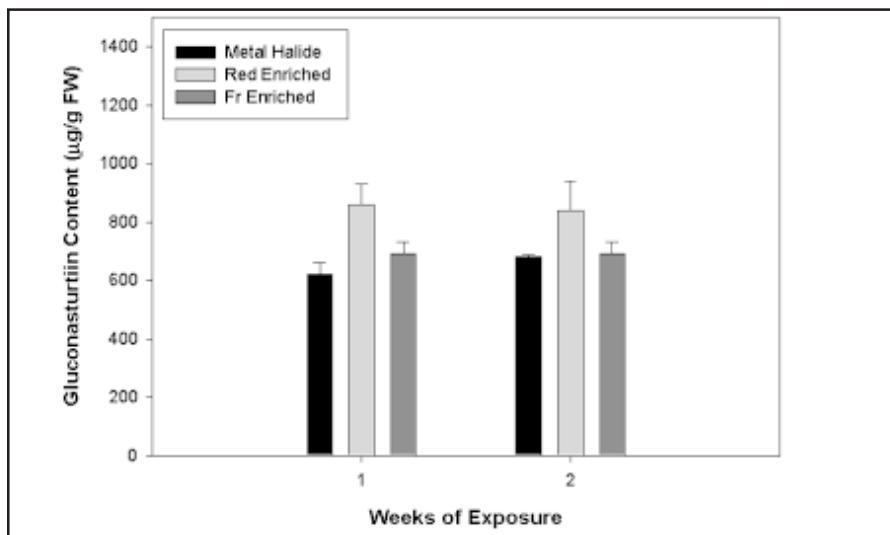


Figure 5. The effects of red- or far-red-enriched light on gluconasturtiin content in watercress. [Exposure to R, FR, or no enrichment (metal halide lamps alone) at the fifth mature leaf stage, grown under long days (16-h day) at a constant 20°C, and PAR from the metal halide lamps of 450 $\mu\text{mol}/\text{m}^2/\text{s}$.]

THE CHALLENGE OF INTERDISCIPLINARY RESEARCH— CHANGING THE PARADIGM

The current model for competitive research funding in the United States is primarily single-principal-investigator grants in a single discipline. As is apparent from the examples cited above, new approaches to the relationships between plants and human health will require collaboration among multiple investigators across several disciplines. At present, funding for this kind of work is rather limited. The United States Department of Agriculture (USDA) competitive grants are generally too small to fund multiple-investigator projects of this type. National Institutes of Health (NIH) grants can be of sufficient size, but generally the scope of such programs has not included agricultural components. The National Center for Complimentary and Alternative Medicine funds important work related to this topic, but its scope and funding base are limited.

It is important to note that plant-derived compounds constitute a major fraction of our mainstream drugs, not just those used in “alternative” therapies. If agriculture is to change its focus from the producer to the consumer in order to remain viable in the United States, and if medicine is to take full advantage of our knowledge-base in plants and nutrition and their role in the prevention of disease as well as cure, we need to define a new paradigm for funding this interdisciplinary work. It is our hope that the Center for Plants and Human Health will help to initiate a national dialogue on this issue. Additional information on Center activities is available at <http://cphh.coafes.umn.edu/>.

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