

# NUTRITION AND METABOLISM PANELS

*[Established in 1966 as Malnutrition Panels; renamed in 1997]*

When the U.S.–Japan Program began in 1965, five panels related to infectious and parasitic diseases were established. But quickly, in 1966, the Joint Committee formally established the Malnutrition Panel to foster and support investigator-initiated research to help alleviate what was then a serious problem of malnutrition. At the time, a range of health problems related to malnutrition was becoming apparent, as the first five-year USJCMSP report indicates:

At the start of the [U.S.–Japan] Program in 1965 evidence was beginning to be available, particularly from studies in Mexico, Guatemala, and South Africa, that early malnutrition was affecting brain development, learning, and behavior of the underprivileged populations of developing countries. There was also increasing evidence that the synergistic interrelationship of malnutrition and infection was responsible for most of the morbidity and mortality of preschool children in these countries as well as the physical retardation encountered.<sup>1</sup>

During the first 5 years of existence, the U.S. and Japanese Malnutrition Panels helped support a range of projects to address these needs: the development of low-cost, protein-rich foods, which included fortifying the foods with amino acids; and biochemical studies of grain crops (rice, sorghum, wheat, and corn), to determine which would provide the greatest yield and protein value.<sup>2</sup> The Panels also helped sponsor the March 1967 International Conference on Malnutrition, Learning and Behavior, which took place in Cambridge, Massachusetts, and which resulted in a book published by MIT Press. Malnutrition Panel members Dr. David Coursin, from the United States, and Dr. Tsuneo Arakawa, from Japan, collaborated “... to develop psychological and neurological methods for evaluating the effects of malnutrition.”<sup>3</sup> Additionally, the Panels supported field studies to assess how malnutrition affects resistance to infection, and began investigations to determine the prevalence of anemia and how it could be prevented.



*Nutrition program in India*

In the 1970s, the Malnutrition Panels continued to support scientific meetings and other projects that focused on prenatal and neonatal malnutrition. These included a January 1974 conference in Guatemala City, “The Latent Effects of Malnutrition and Infection During Pregnancy as a Determinant of Growth and Development of the Child.” In addition, Panel members collaborated in a study of 200 young children, conducted in Chiang Mai, Thailand, which determined that 69 percent of those with severe malnutrition had potentially life-threatening bacterial and viral infections, including pneumonia, otitis media, gastrointestinal infections, skin infections, and sepsis.<sup>4</sup> Also, studies in Thailand indicated that bladder stone disease in children was associated with protein malnutrition, and members of the Malnutrition Panels collaborated in Phase I and Phase II studies to assess whether phosphate supplements were an effective dietary therapy.<sup>5</sup> By the end of the decade, USCJSMSP investigators were conducting studies in animal models to determine the effects of depleting nutrients such as zinc and selenium.

“I joined the U.S.–Japan Program just after its 25<sup>th</sup> anniversary,” said Dr. Hiroo Imura in an August 2004 interview. Dr. Imura, now a consultant to the Japanese Science and Technology Agency, was a member of the USJCMSP Japanese Delegation from 1991–2002. “I was asked by the Ministry of Health

and Welfare to join because my specialty is internal medicine. It is important to have many people in the Program with different expertise.” In Japan, the Ministry of Health and Welfare is one of three government agencies that provides funding for the U.S.–Japan Program.

As the USJCMSP changed during its 40-year history, so did problems relating to nutrition. “At the beginning of the Malnutrition Panel, there were many patients with malnutrition,” Dr. Imura said. “But in the past 40 years, the economic conditions of many Asian countries have improved. There still may be some patients with malnutrition, but many are now facing the problem of *over*-nutrition, especially the problem of diabetes mellitus.” Type 2 diabetes, also called diabetes or late-onset diabetes, is often associated with overweight or obesity. (Type 1 diabetes, also known as juvenile diabetes, is an autoimmune disorder in which antibodies destroy the pancreatic cells that make insulin, and is not associated with obesity).

“Therefore, we changed the name of the Panel from the Malnutrition Panel to the Nutrition and Metabolism Panel, in order to study these problems,” Dr. Imura said. In July 1997, the USJCMSP Joint Committee met in Bethesda, Maryland, and officially changed the name of the Panel. An important emphasis of the Panel’s current research efforts is to identify genetic factors that are associated with diabetes.

In addition to causing tissue and organ damage, diabetes can also increase an individual’s vulnerability to infection. In the United States, an estimated 60 percent of the population is overweight or obese, and approximately 18 million (6 to 7 percent of the population) people 20 years or older have diabetes. In 2000, diabetes ranked as the sixth leading cause of death in the United States.<sup>6</sup> In Japan, diabetes affects more than 7 million people (approximately 6 percent of the population),<sup>7</sup> and is the 10th leading cause of death.<sup>8</sup>

“I was involved in the Malnutrition Panel before I became a Delegate,” said Dr. Fumimaro Takaku in a September 2004 interview. Dr. Takaku, who trained as a hematologist and is now president of Jichi Medical School in Toghigi, Japan, was a member of the Malnutrition Panel from 1982 to 1990. He served as Panel Chair from 1990 to 1992, and

then served as a Japanese Delegation member from 1993 to 2001. “I became Panel Chair in 1990; it is a Japanese custom to give the chairmanship to their most senior members,” he said. Dr. Takaku cited important changes in the Panel during his tenure. “We had been shifting from the problem of mineral deficiencies to health problems such as diabetes and thrombosis that are related to the excess of fat and sugar in the diet. So even within the Japanese Panel, we invited specialists in diabetes or obesity to joint the Panel. That was a big change.”

Throughout its history, the Nutrition and Metabolism Panel has focused on many health problems. Dr. Takaku cited another example. “The difference between Japanese women and U.S. women, with respect to bone density, had not been understood,” he said. “U.S. women have higher bone density than Japanese women.” So the USJCMSP studied differences in bone density between the two groups. “I think it’s one of the very interesting products of the Program,” said Dr. Takaku.

Today, the priorities of the Nutrition and Metabolism Panel reflect the far-ranging need to share information that could benefit the peoples of Southeast Asia. “Our present efforts are focused on enhanced communication between researchers in the U.S. and Japan and, to the extent they are involved, other areas of Southeast Asia,” said Dr. Robert Kuczmarski, in a September 2004 communication. Dr. Kuczmarski is Director of the Obesity Prevention and Treatment Program at the National Institute of Diabetes and Digestive and Kidney Diseases, and U.S. Program Officer for the Nutrition and Metabolism Panel. “We share information on scientific advances and research opportunities related to aspects of basic, clinical, and epidemiological needs and progress in the fields of obesity, cardiovascular disease, metabolic syndrome, and related areas,” he said.

The following is a list of important science advances in research associated with the U.S. and Japanese Nutrition and Metabolism Panels. The list is adapted from information in the USJCMSP five-year reports, as well as information supplied by Dr. Yasushi Saito (Chair of the Japanese Nutrition and Metabolism Panel from 2000–present) and Dr. Robert Kuczmarski (Program Officer for the U.S. Nutrition and Metabolism Panel).

**Nutrition and Metabolism Panels**

[Established in 1966 as Malnutrition Panels; renamed in 1997]

*[Science Advances: 1966–2000]*

- Demonstrated that the use of vitamin C and the production of epinephrine are increased by stress
- Established the significance of vitamin A, iron, and calcium deficiencies occurring in association with the prevalence of malnutrition in Southeast Asia
- Investigated the epidemiology of obesity-associated comorbidities in the United States and Asia. USJCMSP scientists traced the epidemiology and genetics of obesity and its related health disorders in Vietnam and other Asian countries, and compared the information to data from the United States and Japan. The studies revealed that the prevalence of metabolic disorders associated with obesity is increasing in Asian countries, particularly in urban areas.<sup>9</sup>
- Demonstrated the importance of intra-abdominal visceral fat in association with obesity as being predictive of insulin resistance, increased post-heparin plasma hepatic-lipase activity, and mild dyslipidemia. Dyslipidemias are metabolic disorders in which the blood concentration of lipoproteins is too high or too low. Examples of dyslipidemias include elevated blood levels of cholesterol and “bad” low-density lipoproteins (LDLs), and lowered blood levels of “good” high-density lipoproteins (HDL).
- Increased understanding of the pathogenesis of metabolic syndromes. Studies of metabolic syndrome are now emphasized because of its potential risk for the progression of atherosclerosis. USJCMSP investigators clarified that fat accumulation in the visceral area is highly associated with insulin resistance, which leads to metabolic disturbances including hyperlipidemia, hypertension, and impaired glucose intolerance.
- Increased understanding of molecular mechanisms important in metabolic disorders associated with obesity. USJCMSP researchers helped identify molecular mechanisms that link atherosclerosis, insulin resistance, and fat distribution. For example, cytokines secreted from adipocytes in the visceral area, such as adiponectin, leptin, TNF-alpha, visfatin, VEGF, and resistin play key roles in the pathogenesis of metabolic disorders associated with obesity.
- Recognized, through longitudinal studies of risk factors associated with type 2 diabetes (late onset) in Japanese-American families, that the prevalence of impaired glucose tolerance (IGT) and type II diabetes have increased at a greater rate in Japanese Americans than in native Japanese.

- Helped elucidate various biological responses, including inflammation, that play an important role in the progression of atherosclerosis. The bioactive molecules in plasma, such as interleukins, nitric oxide, and C-reactive protein, regulate the function of vascular cells.
- Increased understanding about the relationship between aging and atherosclerosis. The prevalence of arterial calcification increases as a loss of bone mass occurs with advancing age. With aging, the secretion of estrogen decreases, particularly in women. This lack of estrogen stimulates the release of  $\text{Ca}^{++}$  from bone, and promotes the development of atherosclerosis. Excess parathyroid hormone and estrogen deficiency play a crucial role in the aging of arterial tissues.
- USJCMSP scientists collaborated to clone the gene for a key enzyme (25-hydroxyvitamin D-1- $\alpha$ -hydroxylase), which is needed to synthesize the vitamin D hormone. (The active forms of vitamin D are 1,25-dihydroxyvitamin D<sub>3</sub> [1,25-(OH)<sub>2</sub>D<sub>3</sub>] and 1,25-dihydroxy vitamin D<sub>2</sub>, also termed calcitriol.) The studies by USJCMSP researchers also revealed that the promoter region of the enzyme gene has a site that binds parathyroid hormone, which normally regulates the production of vitamin D.
- Identified, cloned, sequenced, and characterized the human SGLT1 gene product responsible for the malabsorption of sodium, glucose, and galactose and accompanying perturbations that may result in severe secretory diarrhea and dehydration.
- Identified a missense mutation (C282Y) of the HFE gene that is homozygous in patients with hereditary hemochromatosis related to HLA class I molecules involved in iron metabolism. (Hemochromatosis is an inherited disorder in which the body absorbs and stores too much iron, which damages organs and may cause them to fail if the condition is left untreated.)

*[Science Advances: 2000–2004]*

- Helped confirm obesity as a worldwide pandemic, which occurs in areas of Southeast Asia, including Vietnam
- Increased awareness of ethnic variation in definition of overweight/obesity. For example, in Japan, obesity is defined by a body mass index (BMI)  $\geq 25.0$ ; in the United States BMI  $\geq 30.0$ . The risk of metabolic disorders is increased in Asians at lower BMI levels than Americans and Europeans.
- Stimulated further research on metabolic syndromes.

### Footnotes — Nutrition and Metabolism Panels

- <sup>1</sup> The United States–Japan Cooperative Medical Science Program: Five Year Report, 1965–1970. U.S. Department of State. Washington, D.C. U.S. Government Printing Office (Stock Number 4400–1370) Released July 1985, p 51.
- <sup>2</sup> This was a time of great excitement due to the so-called “Green Revolution,” which transformed agricultural practices in many countries. The Rockefeller Foundation was very involved in this, with the establishment of the Rice Center, The Maize Center, and other similar initiatives. Ultimately, this work led to such products as High-Lysine corn and the identification of hybrid plants with improved nutritional content. The USJCMSP Panels provided a valuable scientific forum that led to such advancements in this important field.
- <sup>3</sup> Ibid., pp. 51–53.
- <sup>4</sup> United States–Japan Cooperative Medical Science Program—Eighth Annual Report. July 8, 1975. U.S. Government Printing Office. Washington. pp. 6–7.
- <sup>5</sup> United States–Japan Cooperative Medical Science Program—Tenth Annual Report. July 25, 1977. U.S. Government Printing Office. Washington. p. 9.
- <sup>6</sup> National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics. <http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#11>.
- <sup>7</sup> World Health Organization. Diabetes Programme. [http://www.who.int/diabetes/facts/world\\_figures/en/index6.html](http://www.who.int/diabetes/facts/world_figures/en/index6.html).
- <sup>8</sup> Abridged Life Tables for Japan 2003 - <http://www.mhlw.go.jp/english/database/db-hw/lifetb03/4.html>.
- <sup>9</sup> Popkin BM. The nutrition transition and obesity in the developing world. *J. Nutrition*. 2001;131:871S–3S.