

# Foodborne Disease and Public Health

**SUMMARY OF AN IRANIAN–AMERICAN WORKSHOP**

Carol West Sutor and Maria Oria, *Rapporteurs*

Food and Nutrition Board

Office for Central Europe and Eurasia  
Policy and Global Affairs Division

INSTITUTE OF MEDICINE *AND*  
NATIONAL RESEARCH COUNCIL  
*OF THE NATIONAL ACADEMIES*

THE NATIONAL ACADEMIES PRESS  
Washington, D.C.  
**[www.nap.edu](http://www.nap.edu)**

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

This study was supported by Agreement for Services No. 3724 under the International Visitor Leadership Program between the National Academy of Sciences and the Academy for Educational Development. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-11613-8

International Standard Book Number-10: 0-309-11613-9

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, <http://www.nap.edu>.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Suggested citation: IOM and NRC (Institute of Medicine and National Research Council). 2008. *Foodborne disease and public health: Summary of an Iranian–American workshop*. Washington, DC: The National Academies Press.

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**PLANNING COMMITTEE ON FOODBORNE DISEASES AND  
PUBLIC HEALTH: AN IRANIAN-AMERICAN WORKSHOP**

**MICHAEL P. DOYLE** (*Chair*), Center for Food Safety, University of  
Georgia, Griffin

**WILLIAM E. KEENE**, Acute and Communicable Disease Division,  
Oregon Department of Human Services, Portland

**KARL R. MATTHEWS**, Department of Food Science, Cook College,  
Rutgers, The State University of New Jersey, New Brunswick

**J. GLENN MORRIS, JR.**, Emerging Pathogens Institute, University of  
Florida, Gainesville

*Consultant Writer*

**CAROL WEST SUITOR**, Nutrition Consultant, Northfield, Vermont

*Staff*

**MARIA ORIA**, Senior Program Officer

**SANDRA AMAMOO-KAKRA**, Program Associate

**GERALDINE KENNEDO**, Administrative Assistant

**LINDA D. MEYERS**, Director, Food and Nutrition Board

**GLENN SCHWEITZER**, Director, Office for Central Europe and Eurasia,  
Policy and Global Affairs Division



# Reviewers

**T**his report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

**Craig Hedberg**, University of Minnesota School of Public Health,  
Minneapolis

**George J. Jackson**, Food and Drug Administration Alumnus,  
Washington, DC

**Karl Matthews**, Rutgers, The State University of New Jersey,  
New Brunswick

**Ewen Todd**, Michigan State University, East Lansing

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Arthur Reingold** of University of California, Berkeley. Appointed

by the Institute of Medicine, he was responsible for making certain that an independent examination of this summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this summary rests entirely with the authors and the institution.



# Preface and Acknowledgments

**I**n November 2007 the Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) hosted a U.S.–Iranian workshop in Washington, D.C., on the subject of foodborne diseases and food safety. The two-and-one-half day workshop was an important component of a three-week program for Iranian visitors to the United States that was sponsored by the Department of State and carried out with the assistance of the Academy for Educational Development (AED). The program was designed to acquaint 20 Iranian specialists from five universities and research centers with U.S. approaches to the control of foodborne diseases. At the same time, the workshop and other aspects of the program offered the opportunity for a number of U.S. specialists to become acquainted with Iranian approaches to addressing foodborne diseases. The agenda for the workshop is provided in Appendix A; the participants in the workshop are identified in Appendix B.

The workshop was a continuation of U.S.–Iranian cooperative efforts in the field of foodborne diseases that began in 2003. These efforts included three events prior to the 2007 workshop. In June 2003, specialists selected by the IOM and the Iranian Academy of Medical Sciences held a planning session in Les Treilles, France, for joint activities. In October 2004 the first of these joint activities took place: a U.S.–Iranian workshop hosted by the Research Center for Gastroenterology and Liver Diseases of Shaheed Beheshti Medical University in Tehran. The proceedings were published

in 2006.<sup>1</sup> Against this background in cooperation, the Research Center for Gastroenterology and Liver Diseases carried out a jointly designed pilot project during 2006 and 2007 to demonstrate improved approaches to foodborne disease surveillance in a region with a population of 130,000 people centered about 70 miles to the northeast of Tehran. The pilot project is described in this report.

FNB selected the U.S. participants in this workshop. The Research Center for Gastroenterology and Liver Diseases selected the Iranian participants. Representatives from those two organizations jointly developed the agenda for the workshop. See page v for members of the planning committee.

This summary of the workshop proceedings presents the principal issues raised during the presentations and discussions at the workshop. The summary highlights many common interests that Americans and Iranians share in various aspects of controlling foodborne diseases. The summary also addresses topics related to microbiology and cancer that may be of interest for future U.S.–Iranian collaborative efforts.

Following the workshop, the Iranian visitors had the opportunity to continue discussions with a number of U.S. counterparts at their home institutions in the United States and to visit several research, surveillance, and related facilities in the states of Washington, Oregon, and Georgia and in the Washington, D.C., metropolitan area. These facilities are identified in Appendix C. The visits to these institutions were arranged by AED in cooperation with the Department of State and FNB.

As background to provide readers with useful context for some of the content in Chapter 7, “Opportunities for Future Collaboration” a brief description of the current relationship between Iran and the U.S. Historically, the Iranian scientific community has had strong attachments to the U.S. scientific community, but political relations between the two countries have been constrained for some time. In the wake of the attacks on the World Trade Center on September 11, 2001, scientific interactions between the United States and Iran became even more challenging. Obtaining U.S. visas, for example, has been a major obstacle.

The Department of State, as well as the Iranian government and many members of the scientific communities in the two countries, has taken the position that science-related engagement can contribute to solutions of global problems and also help improve understanding of each country’s society and politics.<sup>2</sup> During the past eight years, the U.S. National Academies have sponsored annual U.S.–Iran scientific workshops in both coun-

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<sup>1</sup>National Research Council. 2006. *Food safety and foodborne disease surveillance systems: Proceedings of an American-Iranian Workshop*. Washington, DC: The National Academies Press.

<sup>2</sup>Neureiter, N., and G. Schweitzer. 2008. Engaging Iran. *Science* 319(Jan 18):258.

tries. These workshops and related individual exchanges have shown that cooperation on problems of mutual interest is possible even in harsh political environments. These mutual efforts can build bridges between the two countries.

Special appreciation is extended to the Department of State, which provided financial support for the workshop, and to AED, which arranged the logistics for the visitors to travel from Iran to the United States and within the United States.

The members of the IOM planning committee deserve recognition for their role in developing the agenda, identifying U.S. participants, and planning national visits for the Iranian visitors. The tireless efforts of Mohammad Reza Zali, the director of the Research Center for Gastroenterology and Liver Diseases, to organize the group of Iranian participants and to make the necessary arrangements in Tehran for their visit are greatly appreciated. His contributions to developing the agenda and to making this visit a success were invaluable. Of special importance were the suggestions made by Maria Oria and Linda Meyers, who provided the staff leadership within FNB in organizing the workshop and in preparing this report. Special thanks for her efforts in preparing this summary go to Carol West Suitor.

Lastly, the Iranian and U.S. participants of this workshop deserve full appreciation. This workshop would not have happened without their commitment to science, collaboration, and the improvement of public health.

Glenn E. Schweitzer  
Director, Office for Central Europe and Eurasia  
Policy and Global Affairs Division  
National Research Council



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# Overview

This summary describes a U.S.–Iranian workshop called “Foodborne Disease and Public Health: An Iranian–U.S. Workshop,” which was held in Washington, DC, on November 13–15, 2007. As described in the Preface and in Chapter 1, the workshop was one in a series of cooperative efforts between the United States and Iran. The project of which this workshop was a part was sponsored by the U.S. Department of State with assistance from the Academy for Educational Development.

Foodborne disease surveillance has been a major topic of mutual interest for Iran and the United States. The two countries have collaborated in matters of foodborne disease in the past, with the idea of sharing experiences and knowledge in order to make progress in a field of science that benefits greatly from international cooperation.

The overall objectives of the workshop were to facilitate the exchange of ideas about foodborne disease and public health and to promote further collaboration among Americans and Iranians in this area of mutual interest. With this in mind, the workshop planning committee, in consultation with other participants and the institutions and organizations represented, focused the program on foodborne disease in a broad sense. As reflected in the agenda for this workshop (Appendix A) and in this workshop summary, the planning committee invited experts to address a variety of topics of mutual interest, ranging from the surveillance of outbreaks of foodborne illness to approaches to medical training in the Iranian and U.S. educational systems. Risk assessment methods were included because they can be used as a tool to decide which pathogens

are of most public health concern. Several aspects of cancer and potential relationships of gastrointestinal microorganisms and chronic disease were of special interest to a number of Iranian scientists.

The 11 presenters from Iran and the 10 presenters from the United States represented many different fields of inquiry. Appendix B lists the names and affiliations of meeting presenters and other participants. Appendix C lists the facilities that the Iranian guests visited during their three-week visit to the United States.

## THE WORKSHOP

Michael P. Doyle and Mohammad Reza Zali served as the primary moderators for the workshop. Over the course of the workshop, several Iranian and U.S. colleagues moderated individual sessions. The entire workshop was conducted in the English language, but Iranians had the option of listening to the proceedings as interpreted into Farsi. To foster clear communication, the moderators encouraged attendees to ask questions and to alert speakers of the need to speak more slowly.

After an introduction to the Iranian–U.S. collaborative effort of which this workshop was a part, panels of experts addressed a series of topics: foodborne disease surveillance in Iran and in the United States, selected gastrointestinal diseases in Iran and their investigation, the application of risk-assessment methods to food microbiology, selected aspects of cancer, potential associations of the gastrointestinal microbiota and chronic diseases, and approaches to health education. Periodically, presenters and other attendees took part in lively discussions. During the final session, all participants were invited to express their ideas and suggestions for future collaborative activities.

Chapter 7, “Opportunities for Future Collaboration,” summarizes the lengthy discussion that took place on the last day of the workshop. Throughout the workshop, and especially during the closing session, participants expressed considerable interest in identifying topics for future workshops, in pursuing avenues to initiate cooperative research and other joint activities, and in finding methods to maximize the benefits of collaborative activities between Iran and the United States.

This report is a summary of the workshop presentations and discussions. Appendix D provides a list of abbreviations used during the workshop and in this summary. Meeting transcripts and slides used during presentations served as the basis for the summary, but some of the content has been rearranged for greater clarity. None of the statements made in this workshop summary represents group consensus.



# 1

## Introduction

**T**his workshop on foodborne disease and public health was one in a series of cooperative exchanges between Iranian and U.S. scientists working in these fields. The workshop began with welcoming remarks by several speakers: Michael Doyle, co-chair of the Food and Nutrition Board of the Institute of Medicine (IOM); Glenn Schweitzer, director of the Office of Eastern Europe and Eurasia of the National Research Council (NRC); Linda Meyers, director of the Food and Nutrition Board; and Mohammad Reza Zali of Shaheed Beheshti University of Medical Sciences. This chapter summarizes their descriptions of the objectives of the workshop and also provides background information about the National Academies, the IOM, and U.S.–Iranian cooperation on foodborne disease and public health. In addition, this chapter contains background information on the Iranian health care system that was abstracted from later presentations by Ali Ardalan and Mohammad Reza Zali.

### **SPECIFIC OBJECTIVES**

One specific objective of the workshop was the publication of a summary that would be of interest to specialists in both Iran and the United States. The workshop initially was intended to address issues relating to the prevention of foodborne disease. Given the stated objective and the variety of interests of participants and of the institutions and organizations represented, the workshop planning committee decided to cover a broad range of topics during the meeting. These topics included food-

borne disease surveillance; issues in microbiology, including laboratory testing and the intestinal microflora; the application of risk-assessment methods to food microbiology; selected aspects of cancer; potential associations of chronic diseases with the gastrointestinal microbiota; approaches to medical training and medical-research training; and potentially fruitful forms of further Iranian–U.S. scientific collaboration.

A second specific objective was to help the Iranian guests make lasting contacts with Americans working in the same field. To maximize the effectiveness of the workshop, Schweitzer urged all present to ask questions and make comments and suggestions. In particular, he invited participants to help generate a list of suggestions for future collaborative activities.

## BACKGROUND

### **The National Academies and the Institute of Medicine**

*Presenters: Glenn Schweitzer and Linda D. Meyers*

The National Academies, originally established by the U.S. Congress as the National Academy of Sciences nearly 150 years ago, assist the federal government on questions involving science, engineering, and medicine. The National Academies now comprise four organizations (the National Academy of Sciences, the National Academy of Engineering, the IOM, and the NRC). Besides the many employees of the National Academies, elected members and other experts volunteer their services in the preparation of reports of the National Academies. Many of these reports provide advice for the U.S. government. The international programs of the National Academies work to: (1) improve communication among scientists, engineers, and medical specialists; and (2) promote peace and prosperity and equality around the world.

The IOM was established in 1970 and has approximately 1,600 elected members. The IOM program is organized into nine areas—population health and public health practice; health sciences policy; health care services; global health; food and nutrition; children, youth, and families; African Science Academy development; military and veterans health and medical follow-up; and health policy educational programs and fellowships. Each of these program areas has an advisory board of experts who volunteer their time. The foodborne disease and public health workshop that is the subject of this report was a collaborative effort between the IOM's Food and Nutrition Board and the NRC's Policy and Global Affairs Division.

The National Academies and the IOM probably are best known for

their committee reports—reports written by balanced, expert committees. Such reports undergo a rigorous peer review process and include evidence-based recommendations. In the area of food safety, the IOM has published committee reports on a number of topics, including the safety of genetically engineered foods (NRC, 2004), seafood safety (IOM, 2007), and the safety of new ingredients in infant formula (IOM, 2004). In another vein, the IOM and the Food and Nutrition Board have produced several reports on the prevention of obesity in children. Other types of activities sponsored by the National Academies and the IOM include workshops, roundtables, symposia, and fellowships.

### **Iranian–U.S. Collaboration on Public Health**

*Presenter: Mohammad Reza Zali*

In 1999 a new scientific relationship between the United States and Iran began with a visit to Iran by a delegation from the National Academy of Sciences. During that visit representatives from the two countries agreed that mutual cooperation and education could lead to greater progress for both nations and also serve as the basis for future collaboration. At a subsequent workshop on education held in Italy, participants agreed that, given its importance as an international health issue, foodborne disease would be a suitable subject for an Iranian–U.S. collaboration. Then, at a 2003 meeting in France, a delegation of U.S. and Iranian experts developed plans for a workshop on that subject.

#### *2004 Workshop*

In October 2004 the Research Center for Gastroenterology and Liver Disease of Shaheed Beheshti University in Tehran hosted an Iranian–U.S. workshop on surveillance systems for foodborne diseases. Its purpose was to initiate contacts between Iranian and U.S. experts in order to exchange information about activities in the two countries related to such surveillance systems and also to set up a program for future cooperation. In addition to the Iranian and U.S. experts, representatives from the World Health Organization and the Food and Agriculture Organization participated in the workshop. Participants identified three aspects of foodborne diseases for Iran and the United States to investigate more intensively: surveillance research, international trade, and risk assessment. After the workshop, the U.S. participants visited several production, research, and clinical facilities in the greater Tehran area and continued discussions with their counterparts at those facilities. The next year, in 2005, William E. Keene, a senior epidemiologist from the Oregon Department of Human

Services, and Glenn Schweitzer visited health centers and primary health care units in Iran to increase communication about health care between the two nations. Proceedings from the 2004 workshop were published in 2006 (NRC, 2006).

One result of the 2004 workshop was the establishment of a laboratory for the identification, isolation, and culture of relevant bacterial foodborne pathogens at the Research Center for Gastroenterology and Liver Disease, where the workshop had been held. Later, the Center expanded to include work on various viruses and parasites. Thanks to the teamwork and cooperation of colleagues, the laboratory is now a major center for the evaluation of foodborne diseases and a reference laboratory for the investigation of illness outbreaks.

### **The Health Care System in Iran**

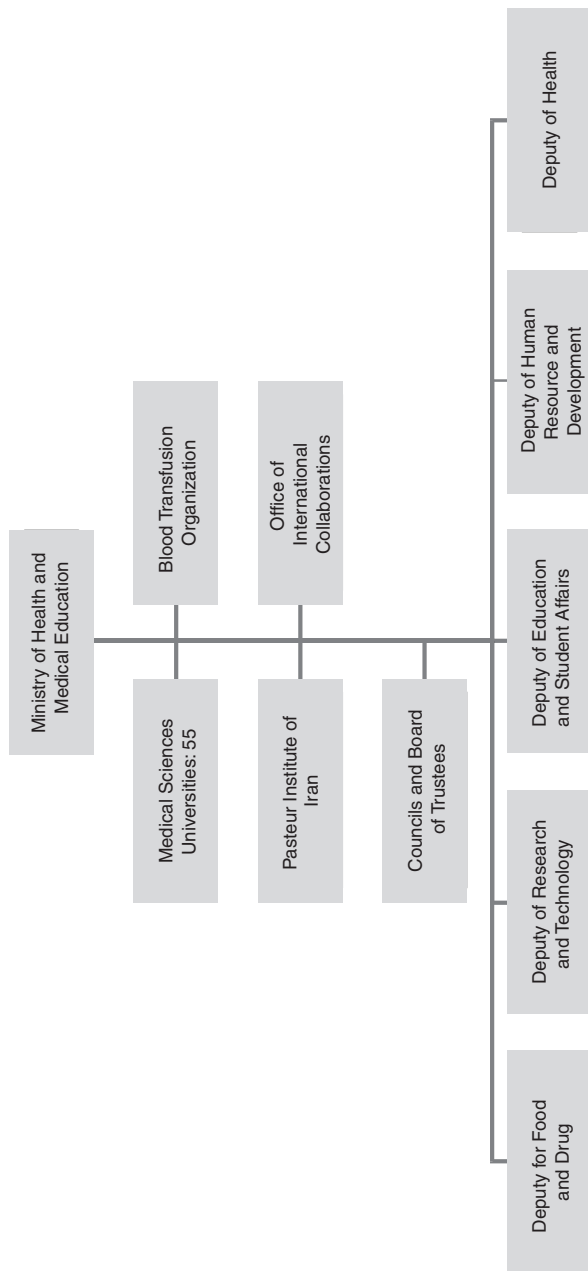
*Presenters: Ali Ardalan and Mohammed Reza Zali<sup>1</sup>*

In Iran, a private health care system works in parallel with the public health care system, but a large majority of the population relies on the public health care delivery system. In the public sector, the Ministry of Health and Medical Education is responsible for health services delivery, medical education, and medical research. Figure 1-1 shows the organizations that fall under the aegis of the Ministry of Health and Medical Education. Notably, the medical education system and the public health service delivery system are integrated.

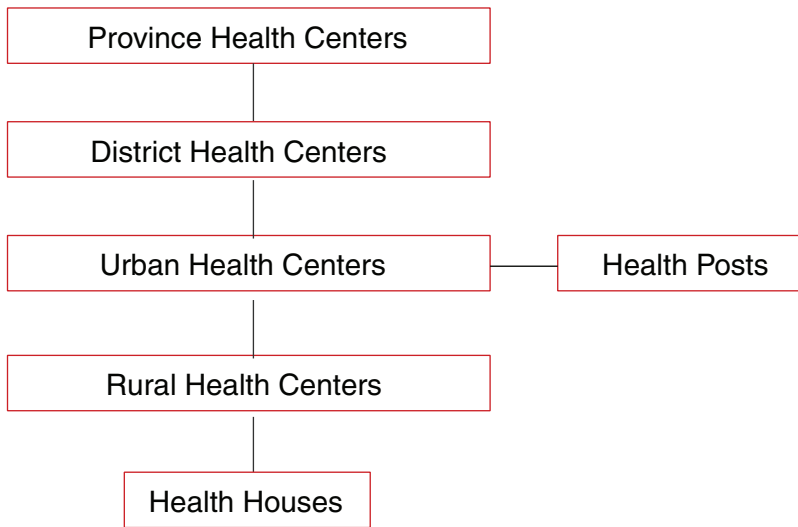
The structure of the Iranian primary health care system is depicted in Figure 1-2. Each of the urban health centers has many satellite units (called health posts) that provide primary health care. The urban health centers also each work with several rural health centers. These centers, in turn, have satellite units (called health houses) that provide primary health care services to surrounding villages. Trained community-health volunteers are an important part of the system. Each volunteer covers 30 to 50 households. Health houses and health posts collect and maintain information on the health of those they serve. The health houses and posts send reports to the health center above them, which, in turn, reports up the line. The health-information system that keeps track of all these data includes such elements as household folders, vital horoscopes (up-to-the-hour accounts of births, deaths, and family-planning activities), log books, and report forms, as well as health network information software.

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<sup>1</sup>This content was abstracted from later presentations by Ardalan and Zali.



**FIGURE 1-1** Organization of the health care system in Iran.  
 SOURCE: M. Zali, Shaheed Beheshti University of Medical Sciences.



**FIGURE 1-2** Structure of the primary health care system in Iran.

### **The Current Workshop**

*Presenter: Mohammad Reza Zali*

With its ongoing modernization, the availability of university and agricultural resources within the country, and a population of more than 70 million people, Iran is evaluating its current status with regard to the control of foodborne diseases and is seeking input from its U.S. colleagues. In addition, the Iranian representatives to the current workshop have a special interest in addressing such conditions as post-infectious irritable bowel syndrome, post-diarrhea arthritis, and post-infectious inflammatory bowel disease—health problems that are increasing in frequency in Iran and that may be linked to the consumption of unsafe food.

Mohammed Reza Zali expressed the hope that this workshop's presentations, productive discussions, and the exchange of views on foodborne diseases and on applications of modern technology and science would advance prevention efforts in both countries.

# Foodborne Disease Surveillance in Iran and in the United States

*Moderator: Mohammad Mehdi Aslani*

Great strides have been made in the surveillance of foodborne disease over the past few years. This chapter covers three workshop presentations related to surveillance in Iran and the United States: Ali Ardalan's description of the Iranian Foodborne Disease Surveillance System Pilot Project, with additional details about laboratory testing provided by Nahid Arjmand Kermani; Robert V. Tauxe's discussion of foodborne disease surveillance in the United States; and Jennifer A. Kincaid's description of PulseNet USA, the national molecular subtyping network for foodborne disease surveillance in the United States. Following the synopses of these three presentations, the chapter concludes with a summary of the group discussion concerning these topics.

## IRANIAN FOODBORNE DISEASE SURVEILLANCE SYSTEM PILOT PROJECT

*Presenter: Ali Ardalan,<sup>1</sup> with Nahid Arjmand Kermani*

Iran is a country with an area of more than 1.6 million square kilometers and a population of approximately 70 million people, 68 percent of whom live in urban areas. It has 30 provinces, 340 districts, and more than 66,000 villages. Iran has nearly 750 hospitals, nearly 8,000 public clinics, and many laboratories, pharmacies, and radiology facilities. The countries

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<sup>1</sup>Ardalan acknowledged contributions from Hamid Mohaghegh.



FIGURE 2-1 Map of Iran.

SOURCE: Reprinted with permission from Britannica Concise Encyclopedia, © 2001 by Encyclopædia Britannica, Inc.

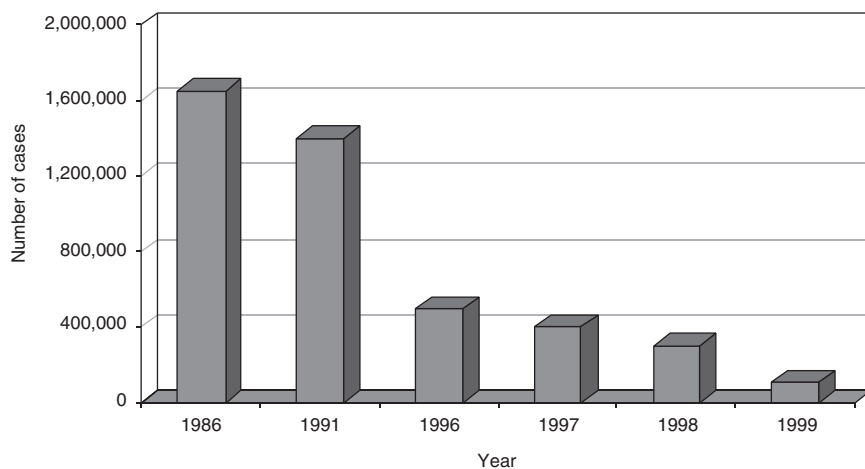
that border Iran—and thus can potentially affect the health of its people—include Afghanistan, Pakistan, Turkmenistan, and Iraq (see Figure 2-1). In his presentation, Ardalan provided background information on surveillance in Iran, described the design and preliminary results of a surveillance system pilot project, identified the limitations and strengths of the surveillance system, and proposed future steps that could improve the surveillance.

### Background on Surveillance

Surveillance data show that Iran has made great strides in improving health. According to Iran's Statistical Center, for example, cases of acute diarrhea per year decreased dramatically between 1986 and 1999: from more than 1.6 million in 1986 to fewer than 115 thousand in 1999 (see Figure 2-2).

Among the foodborne diseases monitored for by Iran's existing surveillance system are typhoid fever, cholera, botulism, and brucellosis. The system requires that any outbreak or epidemic be reported immediately,





**FIGURE 2-2** Number of cases of diarrhea in Iran, 1986–1999.  
SOURCE: Iran's Statistical Center, 2003.

regardless of cause. Figure 2-3 shows the reporting flow for the health care system. (See Chapter 1 for background information on the Iranian health care system.)

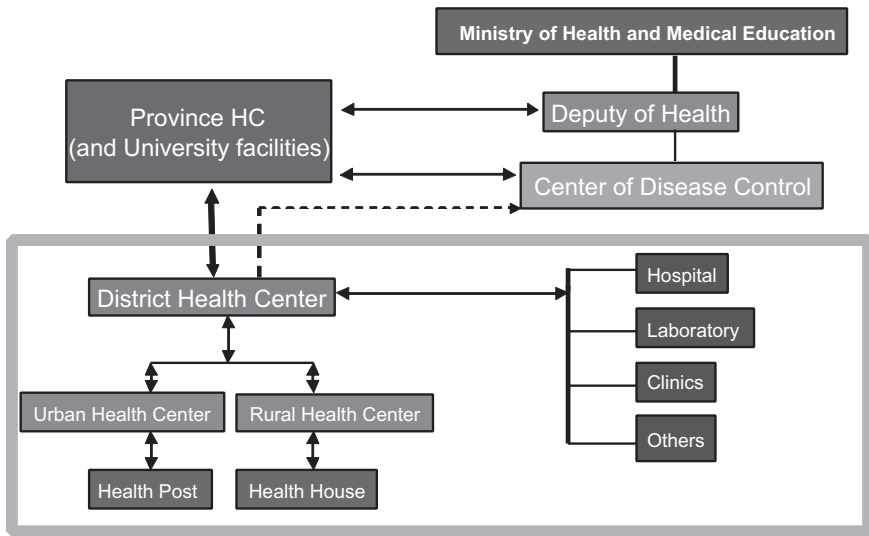
In 2004, 16 foodborne illness outbreaks were reported to the Iranian Center for Disease Control. These outbreaks involved a total of 5,804 cases, 793 of which required hospitalization and 5 of which resulted in death. The most commonly identified pathogens were *Escherichia coli*, *Shigella*, and *Salmonella*. Epidemiological studies were conducted for four of the outbreaks.

Recognizing some limitations of the surveillance system, the pilot project described below was designed to encourage the upgrading of the entire system by integrating lessons learned from the pilot project into the national surveillance system.

### Project Design

The pilot project described by Ardalan was conducted by the Iranian Research Center for Gastroenterology and Liver Diseases. Field coordination and preparation took place in 2006, and the implementation and data collection occurred from March through May of 2007.

The goal of the project was to develop a model for a national foodborne disease surveillance system. The project had four objectives:



**FIGURE 2-3** Iranian health system reporting flow.

NOTE: HC = health center.

SOURCE: Office for Foodborne and Waterborne Disease Prevention Center/CDC, I.R. Iran.

1. Estimate the incidence of diarrhea in pilot sites
2. Determine the etiology of reported diarrhea in the pilot sites
3. Detect and investigate foodborne and other common-source outbreaks in pilot sites
4. Assess trends over time

The pilot sites covered a population of 340,000 people. They were located in Pakdahst, a semiarid region in which 57 percent of the population resides in urban areas, and in Damavand, a cold and humid area in which 74 percent of the population is urban. The case definition for diarrhea in adults was at least three loose stools per 24 hours (compared to previous bowel habits) with the occurrence of the loose stools lasting more than 24 hours. For infants the definition was an increased frequency or decreased consistency of the stool compared to previous bowel habits that the mother considered to be diarrhea.

Data-collection instruments included a questionnaire for diarrhea cases, a stool-sample form, and a case-number reporting form. The questionnaire covered signs and symptoms, treatments, contacts, and risk

factors. A second data-collection form was completed two weeks after the onset of the illness. Recorded data included complications, duration of illness, physician visits, medications, hospitalization, absence from work or school, costs, and whether the illness was fatal.

### Laboratory Tests

During the pilot project, health care staffs were asked to provide a stool specimen for every patient who had a diarrheal episode, preferably within 48 hours after the onset of the illness. Samples were to be obtained before the use of any antibiotic and were not to be mixed with urine. For collecting samples from small children, a diaper swab or rectal swab was suggested. Transport media packaging was specified to allow for the testing of different types of organisms. When possible, staff stored the package at 4°C, and the packages were transported to the Research Center for Gastroenterology and Liver Diseases within 2 to 4 hours.

The laboratory detected a variety of bacterial pathogens in the collected samples, including four categories of *E. coli* (Shiga toxin-producing *E. coli*, enterotoxigenic *E. coli*, enteroaggregative *E. coli*, and enteropathogenic *E. coli*) and also *Salmonella*, *Shigella*, *Yersinia enterocolitica*, and *Vibrio cholerae*. Among the protozoa found were *Entamoeba histolytica*, *Giardia lamblia*, *Cryptosporidium parvum*, and *Blastocystis hominis*. The samples were also tested for rotavirus. Kermani showed slides illustrating the main steps used to detect the organisms, including several steps that used deoxyribonucleic acid (DNA) extraction and polymerase chain reaction.

### Preliminary Results

During the three months of the pilot study, 133 cases were reported, nearly half of which involved children younger than 5 years of age. More than one-third of the isolates failed to exhibit any pathogen after being cultured. Rotavirus and *E. coli* were the most commonly identified pathogens; the reported percentages of *Shigella* and *Salmonella* were much lower. None of the cases required hospitalization or resulted in death. Medical treatment varied: Nearly 60 percent of the patients used antibiotics (which are readily available in Iran without prescription); nearly 50 percent used oral-rehydration solution; about 36 percent used anti-diarrhea/cholinergic medicine; 7 percent used herbal medicine; and another 7 percent used medicine that they had prepared for themselves.

### Limitations and Strengths of the System

A variety of factors may have limited the effectiveness of this monitoring and reporting system. Potential limitations include the underreporting of cases, incomplete cooperation by some patients, incomplete cooperation by the staff (especially during the night shift, when the absence of key personnel may be part of the problem), slow transportation of the stool samples, incomplete pathogen identification, and a lack of precise epidemiologic investigations during outbreaks. A lack of knowledge or technical problems in several areas may explain why many attempts to isolate pathogens, including *S. aureus* and *Campylobacter*, did not yield positive results. These areas include growth requirements and the proper strategies to be used in collecting, transporting, storing, and processing the samples. The consumption of antibiotics by the patients also may have affected the detection of pathogens in their samples.

The major strength of the pilot project is that, as the first Iranian effort to include both field and laboratory capacities, it provides a good starting point from which to improve the foodborne disease surveillance system in the country.

### Closing Remarks—Potential Future Steps

Ardalan proposed a series of steps to improve foodborne disease surveillance in Iran:

- Ensure that the surveillance system has been integrated into the health care system
- Ensure that the surveillance system contributes to real-time decision making by health managers
- Enable the health care system to analyze and interpret the data in the field
- Conduct operational research to ensure the feasibility of the model and its adaptability to the current health care system
- Improve data collection and transfer, data analysis, laboratory testing, and feedback processes
- Improve the ability of the public health care system and of the Research Center on Gastroenterology and Liver Diseases to handle outbreak investigations quickly
- Engage and train the community health volunteers
- Conduct population-based surveys to obtain such information as the incidence of diarrhea and patterns of health utilization
- Design and implement community intervention trials on health education and the prevention of foodborne disease

## FOODBORNE DISEASE SURVEILLANCE IN THE UNITED STATES

*Presenter: Robert V. Tauxe*

### Overview

The Centers for Disease Control and Prevention (CDC), part of the U.S. Public Health Service, is a non-regulatory agency that provides independent scientific assessment to regulatory agencies through the efforts of epidemiologists, microbiologists, statisticians, and other public health professionals. In the 1950s, the CDC established the Epidemic Intelligence Service as an emergency response mission. This program has trained many epidemiologists in the United States and is integral to the agency's mission. One of the CDC's roles is foodborne disease surveillance.

In 1997 the CDC estimated that about 36 percent of diarrheal illness in the United States is attributable to foods. It further estimated that approximately 76 million illnesses, 323,000 hospitalizations, and 5,000 deaths each year are attributable to foodborne illness. The United States has a goal of reducing selected foodborne diseases by 50 percent by the year 2010.

### Core Concepts and Features of Foodborne Disease Surveillance

Public health surveillance is the ongoing and systematic process of collecting, analyzing, and interpreting disease-specific data for use in the planning, implementation, and evaluation of public health practices. In other words, it is a form of monitoring that is linked to action. There are several reasons to conduct foodborne disease surveillance:

- To define the magnitude and burden of diseases that can be prevented or controlled
- To identify outbreaks so that control actions can be taken and new problems can be identified
- To provide a platform for applied research related to foodborne disease
- To measure the effects of control and prevention efforts

In the United States, public health surveillance is complex and occurs at four levels: the clinical level, the county level (approximately 3,500 county health departments), the state level (50 state health departments plus 4 large cities), and the national level (CDC). As illustrated in Figure 2-4, when an ill person visits a health care provider, the flow of information from agency to agency follows a path that depends in part on the disease itself. For some diseases, clinical communication goes straight to the county surveillance office, then to the state epidemiology office and



dard case definitions and makes decisions about which diseases to report nationally. All reporting to the national level is voluntary.

Depending on the purpose of surveillance and the support available, the details of the surveillance can vary in a number of ways including the frequency of data collection, the use of rotating versus periodic surveys, and the use of representative sentinel sites. Such sentinel sites are used to obtain more accurate measurements of trends or of the burden of illness and also for the study of sporadic cases.

### Enhancements to Foodborne Disease Surveillance

Since 1996, foodborne disease surveillance in the United States has been enhanced in a number of ways. These include improvements in notifiable disease reporting in all 50 states, strengthening of the serotyping of *Salmonella* and *Shigella*, the addition of antibiotic resistance monitoring, the initiation of FoodNet (an active sentinel 10-site surveillance system that collects data about sporadic cases), the initiation of PulseNet USA (the national subtyping network for bacterial foodborne pathogens, described in the next section), and the web-based electronic Foodborne Outbreak Reporting System.

With support from the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA), the CDC began FoodNet in 1996. The goals of FoodNet are to determine the burden of foodborne illness in the United States, to monitor the trends in the burden over time, to determine which specific foods and settings contribute to that burden, and to develop and assess interventions to reduce the burden of foodborne illness. FoodNet is a collaborative effort and is guided by a steering team with representatives from the CDC, FDA, USDA, and each of the 10 FoodNet sites. Each of these FoodNet sites is a state or a section of a state that is monitored by the state health department, usually in conjunction with an academic school of public health. In 2003, FoodNet covered 14 percent of the U.S. population. Since FoodNet's inception, the number of pathogens it monitors has increased from 7 to 12; but the very common norovirus is still not covered. The pathogens most commonly identified are *Salmonella*, *Campylobacter*, *Shigella*, *Cryptosporidium*, and *E. coli* O157:H7 (Shiga toxin-producing *E. coli*).

FoodNet uses a variety of methods to estimate the actual number of cases of foodborne illness, which is known to be much higher than the number of diagnosed and reported cases. It performs population surveys to determine the rates of diarrheal illness in the population, the percentage of affected people who seek care, and the percentage of affected people who submit specimens to the laboratory. It also carries out surveys of physicians and laboratories, and it performs active surveillance regard-

ing culture-confirmed cases and data reported to health departments and the CDC. Using the results from these various approaches, the CDC then assigns multipliers to various steps in the process of estimating rates of occurrence. For example, the general multiplier for *Salmonella* is 39, meaning that an estimated 39 cases of *Salmonella* occur for each one that is diagnosed and reported.

**Examining Outbreaks of Foodborne Illness**

Outbreak investigations can act to improve public health by helping prevent additional cases in a current outbreak, by identifying a new pathogen or problem that is involved in the outbreak, and by determining what can be done to prevent future outbreaks. Outbreaks can be detected at any level of the surveillance system. Furthermore, individuals outside the health system may serve a useful role in outbreak detection by serving an “alert function”—for example, by calling the county health department if they suspect a problem of foodborne illness.

Food can be contaminated at any stage, from production and processing to distribution, final storage, preparation, and cooking. The point at which contamination occurs defines the shape of an outbreak. If contamination takes place during final preparation, cooking, or storage, the outbreak will be focused. By contrast, if the contamination occurs during processing, the outbreak will be diffuse, often covering many states. Characteristics of focused and diffused outbreaks are listed in Table 2-1.

The section on PulseNet USA below contains information about an effective new method for detecting a dispersed outbreak.

**TABLE 2-1** Food Outbreak Scenarios

Local/Focused Outbreaks <sup>a</sup>	Diffused/Dispersed Outbreaks
<ul style="list-style-type: none"><li>• Acute large local outbreak</li><li>• High dose, high attack rate</li><li>• Detected locally</li><li>• Local investigation</li><li>• Involves a local food handling error, often egregious</li><li>• Local solution</li></ul>	<ul style="list-style-type: none"><li>• Diffuse, widespread outbreak</li><li>• Low dose, low attack rate</li><li>• Increase in sporadic cases</li><li>• Detected by laboratory-based subtype surveillance</li><li>• Complex multistate investigation</li><li>• Involves an industrial contamination event</li><li>• Industry-wide implications</li></ul>

<sup>a</sup>A series of local outbreaks may be a manifestation of the widespread distribution of a contaminated food product.



## Closing Remarks

Public health surveillance depends on a system of collaborative networks in which epidemiologists work closely with laboratory personnel. The use of public health laboratory subtyping to detect and investigate diffuse outbreaks has been growing in importance. Identifying and investigating new outbreaks and diseases will require a variety of surveillance strategies and a robust and flexible public health capacity.

The following websites provide additional information related to foodborne illness and surveillance:

- FoodNet: <http://www.cdc.gov/foodnet>
- PulseNet: <http://www.cdc.gov/pulsenet>
- Foodborne outbreak surveillance: <http://www.cdc.gov/foodborneoutbreaks>
- CDC Safe Water System: <http://www.cdc.gov/safewater>
- General information about diseases: <http://www.cdc.gov/health>

## **PulseNet USA: THE NATIONAL MOLECULAR SUBTYPING NETWORK FOR FOODBORNE DISEASE SURVEILLANCE**

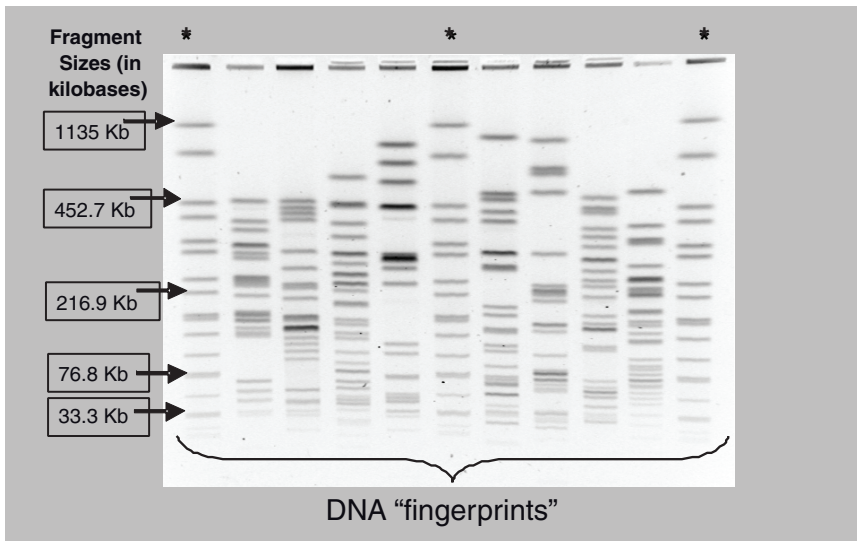
*Presenter: Jennifer A. Kincaid*

### **Description of PulseNet USA**

PulseNet USA, established in 1996, is the national molecular subtyping network for foodborne disease surveillance. Coordinated by the CDC and the Association of Public Health Laboratories, PulseNet USA consists of a national network of state- and local-level public health laboratories and food regulatory agency laboratories. In her presentation, Kincaid provided participants with an informative recent article describing PulseNet USA (Gerner-Smidt et al., 2006).

Laboratories that participate in the network perform standardized molecular typing of foodborne pathogens with pulsed-field gel electrophoresis (PFGE). The CDC houses the resulting databases of PFGE patterns (also called DNA fingerprints), and it makes the databases available to the participating laboratories. Figure 2-5 shows a set of PFGE patterns from *E. coli* O157:H7.

PulseNet USA has two major roles: 1) detecting foodborne disease case clusters through the use of PFGE, which facilitates the early identification of common source outbreaks; and 2) assisting epidemiologists in their investigations of outbreaks by providing case definition, culture confirmation, and a rapid alert system. It is important to note that PulseNet



**FIGURE 2-5** Pulsed-field gel electrophoresis patterns of *E. coli* O157:H7.  
SOURCE: Centers for Disease Control and Prevention, PulseNet USA.

detects clusters, not outbreaks. A PulseNet cluster is a group of patterns that are indistinguishable by PFGE. It is only after epidemiologists investigate a cluster and find epidemiologic links between its cases that the cluster is classified as an outbreak.

The three basic elements of PulseNet USA all involve data: its acquisition, analysis, and exchange. Participating laboratories use the Internet to upload and download information to and from the main database and server located at the CDC. The successful operation of PulseNet depends upon effective communication, comprehensive quality assurance, and reliable quality-control processes.

### **Advantages of Pulsed Field Gel Electrophoresis**

PFGE serves as the current “gold standard” for molecular typing. It has three major advantages:

1. It is highly discriminatory.
2. The universal, relatively simple technique can be used in most laboratories.
3. If highly standardized, PFGE is a definitive subtyping method.

Furthermore, with PFGE the time from receiving the isolate to obtaining the result is satisfactory: approximately 4 days (see the discussion regarding rate-limiting steps in the identification of a source at the end of this chapter).

## **PulseNet USA Activities**

### *Laboratory Network and Databases*

The laboratories that participate in PulseNet USA provide PFGE patterns and demographic data to the PulseNet USA national databases. The CDC manages the databases and produces reports. More than 300,000 PFGE patterns have been submitted to PulseNet USA databases, the largest number of which are for *Salmonella*.

### *Data Analysis—Cluster Search and Detection*

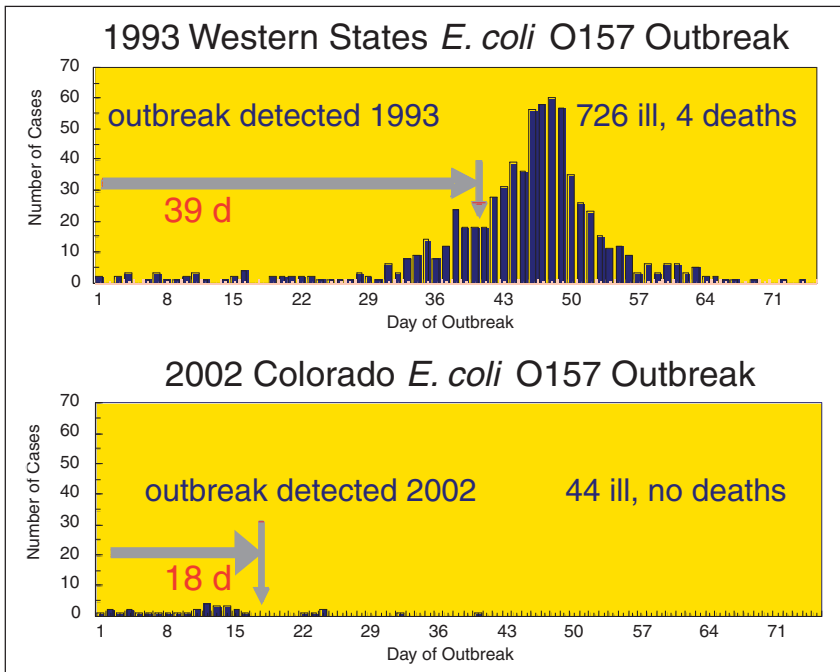
PFGE can be used for molecular subtyping of isolates, which results in an image that is used for analysis. Software tools are used to help compare the PFGE images to find indistinguishable patterns. Cluster detection of cases involves 60-day searches (or, in the case of *Listeria*, 120-day searches). Once a cluster has been detected, the CDC's WebBoard is used to post information about it. Participants can then compare PFGE images and information for the identified cluster with PFGE images and information for the cases from their own local area.

PulseNet has greatly improved the ability to identify and investigate dispersed outbreaks. As shown in Figure 2-6, PulseNet detected a 2002 outbreak of *E. coli* O157 in less than half the time required in 1993. This faster detection allowed for faster recall of contaminated products and helped prevent further illness.

## **International Efforts**

Because the world is now a global community, foods produced in one part of the world may be consumed and cause disease in another part of the world. Consequently, there is a need for effective global early warning systems. Efforts are already underway to establish international collaborations for investigating outbreaks, identifying the sources of problems in laboratories, developing methods to resolve such problems, and developing and validating protocols.

The international family of subtyping networks is growing and now includes PulseNet USA, PulseNet Canada, PulseNet Europe, PulseNet Asia Pacific, PulseNet Latin America, and PulseNet Middle East, which is



**FIGURE 2-6** Illustration of the improvement in the identification of dispersed outbreaks made possible by PulseNet. PulseNet was established in 1996.  
SOURCE: Centers for Disease Control and Prevention, PulseNet USA.

the newest network. At least two representatives from Iran plan to attend an update meeting of PulseNet Middle East in Cairo in December 2007.

### Closing Remarks

The CDC is looking to the future. Its current PulseNet international collaborations include outbreak investigations; addressing various problems with laboratories, analyses, and protocol development and validation; and the development, evaluation, and validation of new typing methods. Among the methods being developed are a simple non-image-based method to use in conjunction with PFGE; multi-locus, variable-number, tandem assay analysis; and single nucleotide polymorphism analysis.

## DISCUSSION

Throughout the session there were opportunities for questions and comments. Some highlights of the discussions are summarized below.

### Standardization of Terminology

Workshop participants discussed the meaning of the term *outbreak*. One definition is the occurrence of an illness at a higher rate than expected, with the expected rate being specific to the particular illness under consideration. In the U.S. foodborne disease surveillance system, an outbreak is defined as two diagnosed infections causing the same illness and being traced to the same food exposure.

Participants noted that perceptions of diarrhea differ around the world and that an international definition could be useful for surveillance purposes. For young children, the mother's report of diarrhea generally is clinically useful. For older individuals, diarrhea is generally said to occur if there is a change in the bowel movement involving increased looseness or frequency of the stool, or both. The Burden of Illness network—a group of people who are conducting FoodNet-like surveys around the world—has been working to develop and validate a standard definition of acute gastroenteritis. Reportedly, they have come to agreement and will publish their definition soon.

### Iranian Foodborne Disease Surveillance

During the discussion it was noted that Iran has a large private health care sector that is distinct from the public system described in Ardalan's presentation.

#### *Outbreak Investigation*

Mohammad Reza Zali noted that in Iran *neither private nor public laboratories or physicians* have a legal obligation to make a report to the public health system when pathogens are found in the stool. Field investigation of outbreaks has tended to come a bit late, and in many cases an epidemiologist has not accompanied the team.

The statistical centers at the Iranian universities each have a physician trained for epidemiological investigation. Each university is responsible for covering a specific area of the country. Outbreaks are reported to a deputy, the deputy reports to the university, and the university reports to the Iranian CDC.

### *Pilot Study*

In response to questions about patient cooperation in the pilot study, Ardalan explained that the most common problem area was obtaining stool samples, and he suggested that educating infected patients about the importance of the samples might help improve cooperation. He also noted that the problem was more common during the night shifts and that the lack of samples at that time might also be related to staffing. Aslani commented that diagnostic laboratories tend to report the result and give it to the patient, but not send the isolate to a public health laboratory.

One of the goals of the pilot project was to convince the Iranian CDC to expand the project nationwide. The pilot study was designed to obtain information to be used in strengthening the capacity for investigations of outbreaks. One aspect of building capacity will be to improve the training of people in the field, including volunteers in small villages.

### *Reduction in Cases of Diarrhea*

The Iranians attribute the remarkable decline in diarrhea from 1986 to 1999 to improvements in their country's water and sewage systems and in sanitation. Cholera was the only reportable disease covered by the earlier data, but, with improved reporting, investigators are beginning to identify other causes of diarrhea.

## **PulseNet and FoodNet**

### *International Opportunities*

A World Health Organization (WHO) program called Global Salmonella Surveillance includes a set of training courses to which many institutions contribute. Another WHO program offers field epidemiology training. Iranians have been actively discussing and planning to participate in this WHO training program.

PulseNet International is developing subtyping networks in different regions of the world (e.g., PulseNet Middle East). Because Iran has a facility for PFGE subtyping, it may be able to take part in PulseNet Middle East in the future. Kincaid explained that PulseNet Middle East is not yet an official network; rather, it still is in development. Currently the main laboratory involved in PulseNet Middle East is the Oman laboratory, which has been receiving training from the only laboratory in the Middle East that is certified through PulseNet International to perform the method (namely, the Navy-Army Research Medical Laboratory in Cairo). Two representatives from Iran (Dr. Amahti Mohammadi, Chief Director of Reference Laboratories, and Dr. Mohammed Rachbar, Department of

Microbiology Reference Laboratories) are scheduled to attend the second meeting on PulseNet Middle East in Cairo in December 2007.

### Testing

Because very many *Salmonella* strains exist, PulseNet USA sets priorities for when to use PFGE on *Salmonella*. Isolates from the common *Salmonella* serotypes receive the highest priority for PFGE subtyping (along with all *E. coli* O157 isolates). *Listeria monocytogenes* also receives priority because PFGE is essentially the only way to identify outbreaks caused by this organism. Outbreaks caused by the rare *Salmonella* serotypes usually can be identified without using PFGE.

PulseNet USA has improved the ability of public health departments to detect clusters of illnesses that may be foodborne disease outbreaks, in part because it brings together subtyping data from many public health departments of states, regions, and countries for comparison. The CDC has developed and standardized the PFGE method, participating laboratories have helped validate the method; the CDC has continuously compared the results and refined the methods as needed, and has published the validated PFGE methods for molecular subtyping of pathogens in PulseNet USA. All PulseNet participating laboratories use standardized protocols, approved equipment, and exactly the same software.

## Identification of the Sources of Foodborne Illnesses in the United States

Of the 1,200 to 1,400 outbreaks of foodborne illness reported each year in the United States, the microbial etiology is determined for approximately 60 percent, and a specific food that was the source of the illness is identified in slightly less than half the outbreaks. In a much smaller number of outbreaks, a specific component of the food may be identified as the source of contamination.

The time required to identify the vehicle of the foodborne illness is highly variable. Clusters of cases reported to a health department may make it possible to determine the cause within a few days, but cluster detection may require weeks, months, or even years. In the United States, new rapid DNA-based subtyping methods are being explored, but they are not yet in common use for *Salmonella* and *Campylobacter*. Since the PulseNet system requires the isolation of the causative agents of foodborne disease outbreaks, there is often a delay of several days to a week in obtaining PFGE results.

The speed of diagnosis and the speed of the reporting system are also

critical. In the United States, the rate-limiting steps may include obtaining stool samples from patients and the laboratory testing of stool samples.

The PulseNet system, which focuses on sporadic cases of foodborne illness, has made it possible to detect food sources that might have been common to cases that are widely dispersed geographically. For example, PulseNet made it possible to identify the contamination of eggs and poultry as contributing factors to acquiring salmonellosis and the under-cooking of ground beef in the home as a risk factor for acquiring *E. coli* O157:H7 infection.



# 3

## Selected Gastrointestinal Diseases in Iran and Their Investigation

*Moderators: Michael Doyle and Mohammad Mehdi Aslani*

A variety of organisms are known to be responsible for foodborne illness, and Iranian researchers have investigated many of them. During the session covered by this chapter, Mohammad Mehdi Aslani described the work of Iranian laboratories that address foodborne illness, Fereshteh Jafari provided an overview of the Research Department of Foodborne and Diarrheal Diseases, Maryam Sanaei discussed work on rotavirus in Iran, E. Nazemalhosseini Mojarad reported on an Iranian study of *Entamoeba histolytica* and *E. dispar*, and Leila Shokrzadeh addressed the distribution of *Salmonella* subspecies in Iran. The Research Center for Gastroenterology and Liver Diseases also has a keen interest in causes of gastrointestinal disease that may not be foodborne; in this vein, Hosein Dabiri Jaldebakhani described the research center's investigations of *Helicobacter pylori*, and Mohammad Reza Zali described the burden of gastrointestinal disease in Iran. Key points from the discussion appear at the end of the chapter.

### **CURRENT TECHNICAL AND SCIENTIFIC ASPECTS OF FOODBORNE DISEASE IN IRAN**

*Presenter: Mohammad Mehdi Aslani*

#### **Overview Related to Foodborne Illness Outbreaks**

In countries around the world, a goal of national health organizations is to protect the health of their countries' populations and to reduce the

toll of infectious diseases, poisons, and chemical and radiation hazards. According to the World Health Organization and the Food and Agricultural Organization, illness caused by contaminated food is one of the world's most widespread health problems.

In 2006 there were 26 foodborne illness outbreaks reported in Iran, but, Aslani said, the extent of the problem is certainly much greater. The 26 reported outbreaks affected nearly 5,000 people and resulted in 11 deaths. The most commonly found causative agent was *Escherichia coli* (type unspecified); other identified causative agents were non-typhi *Salmonella*, *S. typhi*, *Shigella*, *Staphylococcus aureus*, *Entamoeba histolytica*, and rotavirus.

Food production, processing, marketing, and distribution take many forms in Iran. Much of the food handling occurs locally, at the village level, where it is difficult, if not impossible, to implement inspections and other measures to prevent foodborne illness. On the other hand, large-scale food production and industrial food processing come under the purview of the Iranian government. Three ministries are involved in the inspection and control of such processes: the Ministry of Health and Medical Education, the Ministry of Agriculture, and the Ministry of Industry.

### **Iranian Laboratories That Address Foodborne Illness**

Laboratories provide information that is important to the detection and prevention of foodborne disease. The primary means used to identify target organisms in Iran have been older methods that are both slow and labor-intensive. Molecular methods, such as polymerase chain reaction (PCR), are now used to some extent; but the establishment of PCR laboratories throughout the country will require a high financial investment by the government as well as the development of staff training programs, officially approved methods, and national standards. Moreover, PCR results are not definitive: for instance, showing that a toxin gene is present indicates the presence of bacteria but not necessarily the presence of a biologically active toxin.

Ardalan listed several Iranian laboratories involved in the analysis of foodborne diseases, along with the activities that take place in each:

- Food and drug laboratories under the supervision of the Ministry of Health and Medical Education: diagnostic microbiology, virology, and other areas using traditional methods
- Institute Pasteur of Iran: the diagnosis of *Enterobacteriaceae* by traditional and molecular methods, the diagnosis and typing of *Vibrio cholerae*, and the use of molecular typing methods

- Research Center for Gastroenterology and Liver Diseases: a reference laboratory for outbreak investigations, the diagnosis of *Enterobacteriaceae* by traditional and molecular methods, food sample preparation, and the culture and diagnosis of *Campylobacter*
- Iranian veterinary organization laboratories in the Ministry of Agriculture: responsibility for safety related to foods of animal origin
- Institute of Standards and Industrial Research (20 branches throughout the country): facilities for the physical, microbiological, and chemical analysis of food samples

Ardalan called for national laboratories to be established for the study of foodborne pathogens, for the reporting and transport of isolates of specified pathogens to the national laboratories, and for the subtyping of isolates. He also suggested the establishment of both a national and international databank to store subtyping data of isolates of foodborne pathogenic bacteria.

### **Studies Related to Shiga Toxin-Producing *Escherichia coli***

Several studies have been conducted to investigate Shiga toxin-producing *E. coli* (STEC) in Iran (Aslani et al., 1998; Aslani and Bouzan, 2003). Of 2,008 fecal samples screened for STEC in the summer and autumn of 1997, fewer than 5 percent were STEC-positive. In rural areas, individuals carrying STEC were likely to be asymptomatic. Ardalan postulated that the lack of symptoms in people living in rural areas could be the result of contact with livestock and the drinking of unpasteurized milk, resulting in an immunity acquired over time. In urban areas, by contrast, investigators found a significant association between diarrhea and STEC. Children younger than 5 years of age were at the highest risk of infection.

In other studies, fecal samples from cattle, beef samples, and raw milk samples were screened for STEC. About 20 percent of both the fecal samples and the meat samples were STEC-positive, while only 3 percent of the milk samples were. None of the isolates belonged to the O157:H7 serotype.

## **THE RESEARCH DEPARTMENT OF FOODBORNE AND DIARRHEAL DISEASES**

*Presenter: Fereshteh Jafari*

The Research Department of Foodborne and Diarrheal Diseases was established in 2000 under the auspices of the Research Center for Gastro-

enterology and Liver Diseases. Its goal is to better understand the epidemiology of foodborne diseases in Iran in order to provide authorities with information to improve the effectiveness of prevention measures. The department focuses on outbreak investigations, foodborne disease surveillance, the molecular typing of foodborne pathogens, and the microbial analysis of food samples. It also studies the antimicrobial susceptibilities of foodborne pathogens, the development of relevant microbial methods, and the determination of chronic sequelae of foodborne diseases.

The functions of the Research Department of Foodborne and Diarrheal Diseases include the following:

- The isolation and identification of foodborne pathogens
- The serotyping and determination of antimicrobial susceptibility
- Finding patterns of foodborne pathogens using molecular techniques
- The preservation of isolated strains
- The maintenance of its culture collection

Jafari showed slides listing many of the techniques used in the molecular laboratory, from the basic staining techniques to the more advanced molecular biology techniques. He also highlighted the interests and methods of the four reference laboratories for foodborne diseases: bacteriology, virology, pathology, and polymerase chain reaction (PCR) and molecular diagnostics.

The Research Department of Foodborne and Diarrheal Diseases collaborates with the Health System Research Department, which was established in 2005, also within the Research Center for Gastroenterology and Liver Diseases. That department is responsible for collecting and transporting specimens to the Foodborne Laboratory.

A goal of the Research Department of Foodborne and Diarrheal Diseases is to contribute to the control and reduction of foodborne diseases in the population. Part of the department's strategy to achieve this goal is to control foodborne infections acquired at the community level and to control the quality of foods.

The Research Department of Foodborne and Diarrheal Diseases is involved in several international collaborations. These include work with the Swedish Institute of Infectious Disease Control relating to the virulence of diarrheagenic *E. coli*; a project supported by the World Health Organization to investigate the prevalence of soil-transmitted helminthes infection in Tehran province; serving as a reference for a surveillance system; and work with other agencies on enteric bacterial infections and on microbiota in healthy people and in patients with colorectal cancer.

## ROTAVIRUS

*Presenter: Maryam Sanaei<sup>1</sup>*

Viral gastroenteritis is a virus-caused inflammation of the gastrointestinal tract, generally triggered by consuming food or water that is contaminated by viruses that cause vomiting or diarrhea. A large percentage of viral gastroenteritis is caused by a class of viruses called rotavirus. Human feces are the primary source of contamination with rotavirus; respiratory secretions are another source.

Sanaei presented slides covering the morphology, genome, genotyping, classification, pathogenesis, epidemiology, laboratory methods for detection, and prevalence of rotaviruses in Iran. The predominant genotypes in Iran are G4 and G1. A study in the Research Department of Foodborne and Diarrheal Diseases looked extensively at the epidemiology of rotavirus infection and found very high rates of infection among infants and children younger than 2 years of age, with a peak incidence among children 7 to 12 months old. By that age, the passive immunity provided by the mother has decreased, and the children may be exposed through eating or drinking contaminated foods or beverages or by touching toys or other objects contaminated with rotavirus.

Epidemics in Iran typically occur from November to April. In Tehran, Shiraz, and Banderabas, for example, the peak occurs in December; whereas in Mashhad and Tabriz it occurs in February. The peak time appears to vary with climatic factors such as temperature, rainfall, and humidity.

## PREVALENCE AND GENETIC DIVERSITY OF *ENTAMOEBA HISTOLYTICA* AND *ENTAMOEBA DISPAR* IN IRAN

*Presenter: Ehsan Nazemalhoseini Mojarad<sup>2</sup>*

*Entamoeba histolytica* is a parasitic protozoa that is an important foodborne pathogen. In 2006 it was found to be the cause of one of the 26 foodborne illness outbreaks reported in Iran. Relatively little is known about the epidemiology of illnesses caused by this protozoa. Nor is it well understood why disease develops in only 5 percent to 10 percent of the people infected by these amoebas. Possible reasons include a spectrum

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<sup>1</sup>Sanaei acknowledged the contributions of Houtan Radpour, Reza Mohebi, and Mohammad Reza Zali.

<sup>2</sup>Mojarad acknowledged the contributions of A. Haghighi, B. Kazemi, and Mohammad Reza Zali.

of virulence among the *E. histolytica* strains and variability in the host immune response against amoebic invasion.

In a study carried out over the past several years, Iranian scientists investigated the variation in *E. histolytica* and *E. dispar* isolates using a PCR assay. Because the microscopic identification of *E. histolytica* is insensitive and inaccurate, differentiation requires molecular methods.

The objectives of the study, as reported by Mojarad, were

- to determine the prevalence of *E. histolytica* and *E. dispar* in stool samples of patients with gastrointestinal disorders; and
- to identify the genetic variation of *E. histolytica* and *E. dispar* isolates.

Specific questions included: How genetically polymorphic are the Iranian isolates? How similar are the genotypes of the Iranian strain to the genotypes of other *Entamoeba* strains?

From July 2005 to January 2007, the investigators collected 3,826 fecal samples from three different areas of Iran. Mojarad briefly described the methods and showed slides covering the sample collection by sex and by geographic area, the frequency of *E. histolytica* and *E. dispar* by geographic region, and PCR and sequencing results.

The investigators found no significant association between infection and diarrhea or other intestinal disorders. Similarly, no significant associations were found between age, sex, or members of the family and the prevalence of *E. histolytica* or *E. dispar*. All Iranian asymptomatic cyst passers were infected by *E. dispar*, a finding that agrees with results from several other studies in Iran. The PCR results were in close agreement with worldwide PCR sequencing analysis.

In closing, Mojarad mentioned limitations of the study, including the small number of assays positive for *E. histolytica*.

## DISTRIBUTION OF *SALMONELLA* SUBSPECIES IN IRAN

Presenter: Leila Shokrzadeh<sup>3</sup>

*Salmonella* is an important zoonotic pathogen that can be spread to humans through many kinds of foods. A *Salmonella* infection typically causes fever, diarrhea, and gastroenteritis. In his presentation, Shokrzadeh provided an overview of recent outbreaks of salmonellosis, a collection of

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<sup>3</sup>Shokyzadeh acknowledged the contributions of S. Modorresi, M. Tajbakhsh, and Mohammad Reza Zali.

results from the testing of fecal specimens and selected foods, and information regarding the susceptibility of the organisms to antibiotics.

In 2006, three notable *Salmonella* outbreaks were reported in Iran from different parts of the country. In the first, 65 people were infected by *S. typhi* from water; in the second, 250 people were infected by non-typhi *Salmonella* in food; and in the third, 15 people were infected by non-typhi *Salmonella*. One death was reported.

Between 2003 and 2005 in Tehran, various *Salmonella* serotypes were detected in 6.3 percent of stool samples obtained from patients with diarrhea. When fecal samples were tested from children with diarrhea from many parts of Iran, *Salmonella* was isolated from fewer than 5 percent of the samples.

For the food supply, testing found that about 20 percent of the meat samples and 45 percent of the chicken samples were contaminated with *Salmonella*. *Salmonella* Thompson was the most prevalent serotype in both meat and chicken. A study of equipment and surfaces in meat markets detected *Salmonella* contamination in 12 percent of the markets. A study of chickens found that 68 percent of the animals were infected with various *Salmonella* serotypes, with Paratyphi C the most prevalent serotype. In a sample of 500 local and 500 commercial eggs, 0.8 percent of the local eggs cultured positive for *Salmonella* species.

Investigators found considerable antibiotic resistance in the non-typhi *Salmonella* serotypes, especially to nalidixic acid, trimetoprim sulfamethoxazol, and tetracyclin. The organisms were most likely to be sensitive to ciprofloxacin, ceftazidim, cefotaxim, and gentamicin.

Related ongoing projects conducted by the Research Center for Gastroenterology and Liver Diseases include the phylogenetic analysis of various *Salmonella* serotypes in Iranian isolates and the investigation of extended-spectrum beta-lactamase-producing bacteria in various isolates.

## **HELICOBACTER PYLORI IN IRAN**

*Presenter: Hosein Dabiri Jaldebakhani*

Infection with *Helicobacter pylori* is highly prevalent in Iran. Although it has not been established that this bacterium is transmitted through food or water, *H. pylori* is of great importance to health because it causes damage to the gastric structure, often resulting in peptic ulcers and sometimes in other serious health problems, including gastric cancer. Many infected individuals show no overt evidence of disease. Dabiri reported on work being done by a group at the Research Center for Gastroenterology and Liver Diseases that focuses on *H. pylori*.

The Research Center for Gastroenterology and Liver Diseases group

diagnoses *H. pylori* infection using two general methods: various invasive tests that require biopsy through an endoscope; and less invasive tests, mainly the urea breath test, serological tests, and stool antigen tests. Both a seroepidemiologic study and a histopathology study found that the prevalence of *H. pylori* infection in middle-aged and older adults in different parts of Iran was nearly 90 percent (Malekzadeh et al., 2004). Studies with *H. pylori* in culture found that patients with ulcers and those without ulcers had similar prevalences of infection (close to 60 percent).

Dabiri presented slides giving information about reinfection rates, which appear to be approximately 20 percent (Zendehdel et al., 2005); antibiotic susceptibility; molecular typing; and possible relationships between *H. pylori* genotype and disease. He showed, for example, that the Iranian genotype in *H. pylori* is consistent with the European genotype, which has low to mid-level risk for the development of gastric cancer.

The Research Center for Gastroenterology and Liver Diseases has a number of ongoing projects related to *H. pylori*, including the following:

- An effort to identify *H. pylori* in Iranian patients with gallstones, atherosclerosis, and chronic sinusitis
- A prospective study on the recurrence and treatment failures of *H. pylori* infections
- An evaluation of non-*pylori Helicobacter* bacteria in clinical samples
- A study of how *H. pylori* interacts with selected non-pathogenic bacteria in an effort to identify probiotics
- A determination of antibiotic resistance mechanisms in *H. pylori* in Iranian isolates
- A restriction-fragment-length polymorphism study of selected virulence genes of *H. pylori* strains that have been isolated from Iranian patients with and without gastric ulcers

## THE BURDEN OF GASTROINTESTINAL DISEASE IN IRAN

Presenter: Mohammad Reza Zali

### Overview

The purpose of assessing the burden of gastrointestinal disease in Iran is to help guide strategies for its prevention and treatment. Gastrointestinal disorders pose a huge burden on society. One out of every 10 patients who consult a general practitioner in Iran has a gastrointestinal problem. Among the conditions commonly seen in Iran are various forms of gastrointestinal cancer, liver diseases, and a variety of upper and



lower gastrointestinal tract disorders. In particular, Mohammad Reza Zali identified inflammatory bowel disease as highly prevalent. Among the diseases that are increasing in incidence are esophageal and colorectal cancer, hepatitis C, nonalcoholic fatty liver disease, cirrhosis of the liver, Barretts esophagus, pancreatitis, gallstones, diverticular disease, celiac disease, and irritable bowel syndrome.

### **Study Description**

To obtain current and accurate information on the burden of disease in Iran, Mohammad Reza Zali and colleagues designed a study under the sponsorship of the Shaheed Beheshti University in Tehran. Data were collected over a period of 12 months. Approximately 15,000 individuals were randomly selected from a population of approximately 5.2 million people from both urban and rural settings. These individuals were invited to complete a questionnaire interview and have a clinical examination. The questionnaire covered gastrointestinal signs and symptoms experienced in the previous 6 months, medical history, indicators of the severity of the disorder and of the use of health care services, medication use, demographics, and selected opinions.

A validated questionnaire was used in a smaller cross-sectional study that took place from May 2006 to July 2007; 7,150 subjects were randomly selected to participate from a general population of approximately 400,000 people from Damavan, Firozkoh, and Pakdasht.

### **Study Results in Brief**

Zali showed slides on the prevalence of a large number of gastrointestinal diseases. Gastrointestinal esophageal reflux disease (GERD) and functional abdominal bloating are very common, with prevalence rates that are much higher in females than in males and much higher in middle-aged and older adults than in young people. Of people affected by irritable bowel syndrome, more than 60 percent also had GERD. Of people with GERD, 34 percent also had irritable bowel syndrome. Older subjects were significantly more likely to have both diseases. This strong association between the two diseases—an association that appears to be less common in more developed countries—warrants further study.

Because Iran started a vaccination program against hepatitis B nearly 15 years ago, nearly all the people with hepatitis B infections were older than 20 years of age. Beginning in the fifth decade of life, the mortality rate for gastrointestinal disease in Iran increases sharply with age; and it is high overall. Gastric cancer is the largest single contributor to gastrointestinal disease mortality.

Considering the high prevalences of *H. pylori* (as discussed in the previous section) and of GERD, it could be useful to study their contributions to the development of esophageal cancer in the Iranian population.

## DISCUSSION

*Moderator: Mohammad Mehdi Aslani*

During the discussion period, participants raised questions regarding the methods used for detecting Shiga toxin-producing *E. coli* (STEC) and concerning the testing that was conducted on cattle feces and foods. Aslani explained that the study on STEC in Iran did not provide a basis for determining whether the STECs are capable of causing disease in humans.

Mohammad Zali stated that the purpose of the study investigating the genotype and prevalence of rotavirus infection was to obtain information for a potential vaccination program.

Participants also raised questions about different forms of hepatitis and their possible relationship to liver disease in Iran, about possible connections between foodborne pathogens and the long-term diarrhea associated with inflammatory bowel disease, about studies comparing traditional medicine with antibiotic therapy in the control of diarrhea (none has been done), about the prevalence of norovirus infections in Iran (data unavailable), about the sources of antimicrobial resistance (e.g., self-medication with antibiotics suspected), about associations of amoebic infections in patients with *Salmonella* or a viral infection (no information), and about screening for sapoviruses (not routine in the United States). Responding to Keene's comments that half or more of the diarrheal outbreaks in the United States are due to norovirus, Mohebbi discussed the limitations in Iran's detection system for noroviruses that may contribute to that country's low reported rate of norovirus infection. Beuchat reported on the increase in the percentage of foodborne illness outbreaks attributable to fresh and fresh-cut produce in the United States—a potential food source of illness that has not yet been investigated in Iran.

Miller emphasized that the diversity in the production, processing, and distribution of foods in Iran needs to be considered in developing and implementing foodborne illness prevention efforts.

# 4

## Applying Risk Assessment Methods to Food Microbiology

*Moderator: Karl R. Matthews*

In deciding how to deal with problems relating to foodborne illness, two useful sets of tools are risk-assessment methods and methods for weighing trade-offs between competing risks. The workshop had presentations on each, with Robert L. Buchanan discussing risk assessment methods and Richard A. Forshee describing the evaluation of risk-risk trade-offs. This chapter covers both their presentations and then ends with highlights of the subsequent discussion.

### RISK ASSESSMENT METHODS

*Presenter: Robert Buchanan*

#### Risk Assessment Overview

Risk assessment is a method for applying pertinent scientific data to make risk-management decisions. High-quality risk assessments identify clearly what is and what is not known; they characterize how well the data are known, taking into account the variability and uncertainty in the data; and they are sufficiently transparent to reveal possible biases or errors in reasoning. Such risk assessments provide a powerful tool for estimating the effects of potential options and food safety standards on the risk that is being addressed.

Risk assessments can be grouped into four general classes based on

the extent to which the treatment of the data is quantitative. These four classes are

1. formal expert elicitations;
2. qualitative assessments that use non-numerical descriptors;
3. semi-quantitative assessments that combine quantitative data and non-numerical descriptors; and
4. quantitative assessments in which mathematical modeling uses a large amount of scientific data.

Although semi-quantitative assessments are the most widely used of these classes, Buchanan focused on quantitative methods.

### **Quantitative Microbial Risk Assessment**

A quantitative microbial risk assessment produces a mathematical statement that is based on the cumulative probabilities of certain adverse events happening following an exposure to a hazardous agent. The result of such a risk assessment includes not only an estimate of the risk but also an estimate of the attendant uncertainties. In addition to the quantitative factors, the assessment will also generally consider qualitative factors in its discussion of risk and uncertainty.

Quantitative microbial risk assessments are generally of two basic types: deterministic and probabilistic. Deterministic assessments use point estimates to describe risk at a certain level of exposure (for example, the mean risk or the 95th or 99th percentile of risk). A disadvantage of this approach is that it may overestimate risk if one tries to combine factors. Probabilistic assessments use entire distributions and require advanced modeling techniques, such as those made possible with Monte Carlo simulation software. Using a Monte Carlo simulation, for example, one could determine the impact of changing the refrigerator temperature on the growth rate of a pathogenic microorganism and, therefore, on the final risk posed by an organism in a food.

The advantages of probabilistic models include more accurate results, the ability to modify the model easily to incorporate new data, the ability to produce “what-if” scenarios, and the ability to evaluate the effects of potential actions to mitigate risk. In a “what-if” scenario, one can make substitutions in the model that make it possible to examine how making a specific change would affect an outcome. One disadvantage of probabilistic assessments is that they may be difficult for risk managers to interpret.

Microbial risk assessment could be used in a variety of ways by the U.S. Food and Drug Administration (FDA). Some possibilities are

- setting priorities;
- identifying steps that are major contributions to risk;
- evaluating the effectiveness of potential control measures, standards, and criteria;
- evaluating the contribution of compliance to risk management;
- determining subpopulations at increased risk; and
- assessing uncertainty and variability.

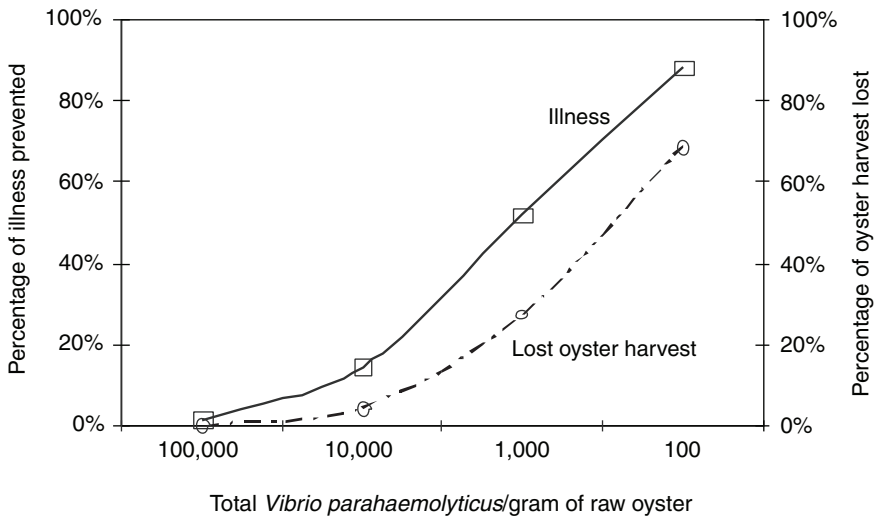
## Types of Microbiological Risk Assessments

### *Risk Ranking*

Risk ranking is a technique used to compare relative risks. It can be used to compare different foods for a single hazard, different hazards for a single food, and, potentially, multiple hazards and multiple foods. In general, the purpose of risk ranking is to help establish priorities, as in developing a budget. Recently, for example, a quantitative assessment was conducted on the relative risk to public health from *Listeria monocytogenes* in 23 classes of ready-to-eat foods, such as delicatessen meats and certain cheeses, in the United States (DHHS/USDA, 2003). As part of that assessment, the assessors estimated the risk per serving and the predicted number of cases of listeriosis per year for the total U.S. population. The results are being used to focus inspection activities, surveillance activities, educational strategies, research, and new risk assessments.

### *Product/Pathogen Pathway Analysis*

Product/pathogen pathway analysis is a technique that can be used to examine factors that contribute to risk over the course of a particular segment of the path from farm to table. It makes it possible to quantify the importance of contamination sources, the effectiveness of interventions, the comparative effectiveness of different control measures, the likely effect of performance criteria or standards, and the importance of complying with the criteria. One example of product/pathogen pathway analysis is described in a recent report on *Vibrio parahaemolyticus* in raw oysters (CFSAN, 2005). The analysis assessed the importance of various possible contributing factors, such as the concentration of the organism in the environment, the length of time the oysters went without refrigeration, the number of grams of oysters consumed, the region of the United States, and the season. Figure 4-1 illustrates how varying the standard for the concentration of the organism allowed in oysters would affect the percentage of illnesses prevented and the percentage of the oyster harvest that would be lost. This type of information is valuable to decision makers.



**FIGURE 4-1** Effects of the concentration of *Vibrio parahaemolyticus* in oysters on the percentage of illness prevented and the percentage of the oyster harvest that would be lost.

SOURCE: CFSAN, 2005.

### *Geographical Risk Assessment*

Geographical risk assessment, sometimes called epidemic risk assessment, estimates the effect of introducing a new hazard into a geographical area. This type of risk assessment involves modeling the factors that affect the introduction of a disease agent, the ability of an infection to be self-sustaining in a population, the factors that affect the rate of dissemination of the infection, and the degree to which mitigation activities disrupt the dissemination. An example of such a geographical risk assessment is the Harvard bovine spongiform encephalopathy (BSE) risk assessment ([http://www.fsis.usda.gov/Science/Risk\\_Assessments/index.asp#BSE](http://www.fsis.usda.gov/Science/Risk_Assessments/index.asp#BSE)). It analyzed the potential spread of BSE among cattle if BSE were to be introduced into the United States and the resulting potential for humans to be exposed to contaminated material.

### *Risk–Risk Assessments*

Risk–risk assessments are performed when reducing the risk of one hazard can be expected to increase the risk of another. One current example is the FDA's examination of the risk posed by the methyl mercury in

fish compared with the risks caused by decreased intake of omega-3 fatty acids if fish consumption is curtailed. To date, risk–risk assessments that involve food microbiology have been qualitative rather than quantitative. Among the challenges of risk–risk assessments are finding a common end point for comparison and redefining a benefit as a risk.

### Closing Remarks

All risk assessments have finite life spans. As new data emerge, new assessments are needed. Many useful resources are available to provide guidance in conducting high-quality microbial risk assessments. A number of them are listed in Box 4-1.

#### BOX 4-1 MICROBIAL RISK ASSESSMENT RESOURCES

##### Publications

1. Brown, M., and M. Stringer. 2002. *Microbiological risk assessment in food processing*. Cambridge, UK: Woodhead Publishing, Ltd.
2. Center for Food Safety and Applied Nutrition, Food and Drug Administration. 2002. *Initiation and conduct of all “major” risk assessments within a risk analysis framework*. A Report by the CFSAN Risk Analysis Working Group. <http://www.cfsan.fda.gov/~dms/rafw-toc.html> (accessed February 5, 2008).
3. Haas, C. N., J. B. Rose, and C. P. Gerba. 1999. *Quantitative microbial risk assessment*. New York: Wiley & Sons.
4. Schaffner, D. W., ed. 2008. *Microbial risk analysis of foods*. Washington, DC: ASM Press.
5. Vose, D. 2000. *Quantitative Risk Analysis, 2nd edition*. New York: Wiley & Sons.

##### Websites

6. Food and Agriculture Organization/World Health Organization Joint Expert Meetings on Microbiological Risk Assessment: <http://www.codexalimentarius.net/web/jemra.jsp>
7. Joint Food and Agriculture Organization/World Health Organization Food Standards Program. *Codex Alimentarius*: [http://www.codexalimentarius.net/web/index\\_en.jsp](http://www.codexalimentarius.net/web/index_en.jsp)
8. Joint Institute for Food Safety and Nutrition
  - Risk analysis training: [http://www.professionalstudies.umd.edu/food\\_safety/](http://www.professionalstudies.umd.edu/food_safety/)
  - Risk Assessment Clearinghouse: <http://www.foodrisk.org/>

## EVALUATION OF RISK–RISK TRADE-OFFS

*Presenter: Richard A. Forshee*

A food or nutrient may increase some risks and decrease others. In his presentation, Forshee described an integrated approach for comparing the benefits and risks of consuming a nutrient or food, including a proof of the concept. He also distinguished between risk-based and safety-based approaches.

### **Application of an Integrated Approach**

A review by Cohen and colleagues provides an example of an integrated approach to risk–risk assessment as applied to fish consumption (Cohen et al., 2005). The analysis looked at both the adverse effect that methyl mercury may have on the development of the brain and nervous system and the benefits that n-3 polyunsaturated fatty acids have in reducing the risk of coronary heart disease among older men and women. In doing so, the analysis explicitly recognized that the risks and benefits of fish consumption may vary across subpopulations.

As described in the paper, the risk–risk assessment examines exposures, dose–response relationships, and both positive and negative health endpoints. After converting those health endpoints to a common scale, Quality-Adjusted Life Years (QALYs),<sup>1</sup> Cohen and coworkers then estimated the QALYs gained under five different scenarios. The scenarios differ in the population and fish consumption levels.

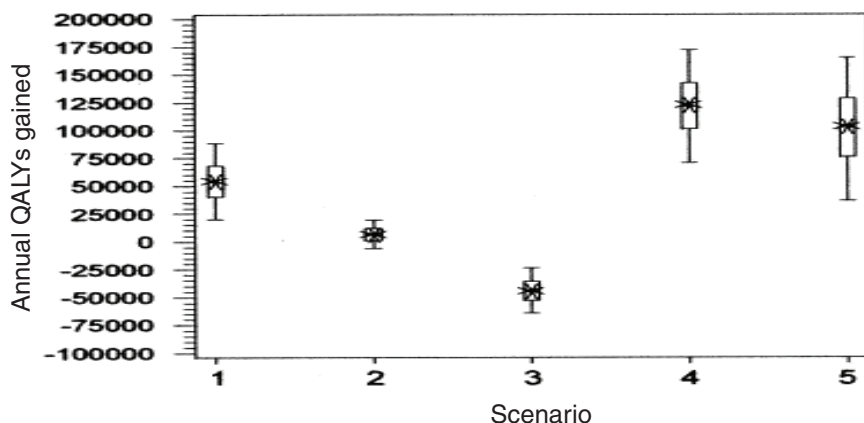
As shown in Figure 4-2, the most favorable overall results in terms of QALYs gained occur in scenarios 4 and 5, both of which involve a 50 percent increase in total fish consumption. The other scenarios, which produced gains of fewer QALYs, called for women of childbearing age to reduce fish consumption or to switch to fish low in methyl mercury or else for the entire population to reduce fish consumption. This type of analysis can help policy makers evaluate specific risks and examine the effects of different actions by the public on public health.

Another analysis of the risks and benefits of fish consumption (Ponce et al., 2000) used a somewhat different method and produced curves showing QALYs as a function of fish consumption measured in grams per day. That analysis found that the only situation in which fish consumption

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<sup>1</sup>The Quality-Adjusted Life Year (QALY) is an index that combines the quantity and quality of life. It assigns a value of 1 to one year of “perfect” health-life expectancy and assigns a value of less than 1 to one year of less than perfect life expectancy. Death is assigned a value of 0.





**FIGURE 4-2** Annual Quality-Adjusted Life Years (QALYs) gained by type and amount of fish intake. Key to scenarios: (1) Women of childbearing age switch to fish low in methyl mercury ( $\leq 0.13$   $\mu\text{g}$  of methyl mercury/g of fish); (2) women of childbearing age reduce total fish consumption by 17 percent; (3) entire population reduces total fish consumption by 17 percent; (4) women not of childbearing age and all men increase total fish consumption by 50 percent; and (5) all women and all men increase total fish consumption by 50 percent.

SOURCE: Cohen et al., 2006.

results in a reduction in QALYs is when people eat large amounts of fish that are high in methyl mercury.

### Proof of Concept

Forshee used data and approaches from the article by Cohen et al. (2005) to try to provide a proof of concept concerning coronary heart disease and intelligence quotient (IQ, which is one measure of brain development) as related to fish consumption measured in servings per week. Using data and approaches taken from the article by Cohen and coworkers, he examined the QALY loss for women ages 15 years and older as a function of fish consumption measured in servings per week. (No risk of harm was observed in men.) By combining the lost QALYs from coronary heart disease and from loss of IQ points, Forshee found that the greatest benefit (reduction in QALY loss) occurs when fish consumption is increased from zero to one serving per week. At higher intakes, there is much more uncertainty about the effect of additional fish consumption on QALY loss.

Forshee noted that his analysis has a number of limitations, includ-

ing those of the Cohen article, the fact that only two health endpoints are being considered, the fact that the analysis assumes a constant level of fish consumption over a lifetime, and the large width of the confidence intervals (because he did not use a Monte Carlo approach in estimating them).

The approach described above could be useful in examining a variety of risks, such as those related to alcohol consumption, sunshine exposure, and food fortification (which might increase the intake of nutrients above a safe level). Although Forshee believes that the approach holds much promise, he said that it also has some limitations. QALY is far from being accepted as a common metric, for example, and some people do not think it is appropriate to use a common metric for diseases that affect children and those that affect the elderly. Furthermore, the uncertainty that is identified in the calculations can make decision making difficult. Nonetheless, the approach states the uncertainty more explicitly than is typical in the risk-assessment arena, which can be seen as an advantage. One practical limitation is that this type of approach may not be usable in regulatory matters without changes in regulatory law. Also, importantly, risks have attributes that affect how people perceive them. For example, does the risk stem from a natural component of food or from a contaminant? Is it a familiar risk or a new risk? All of these factors can affect risk communication and management.

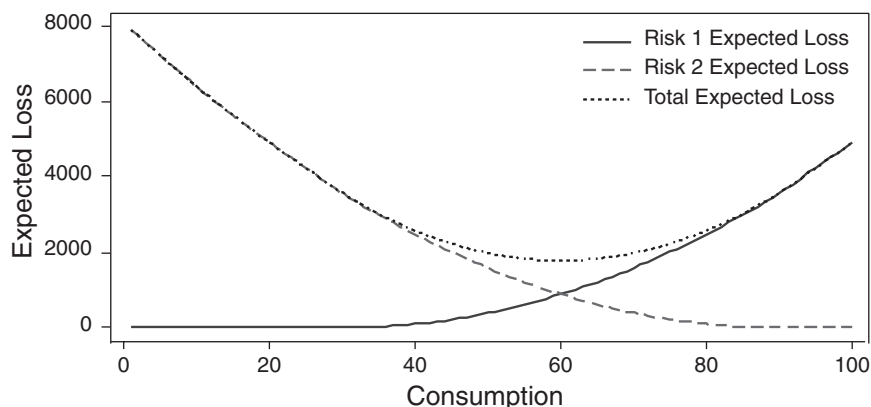
### **Risk Versus Safety**

Many regulatory approaches are based on establishing *de minimis* safety levels for exposure or consumption—intake levels that are believed to carry no risk. For nutrients, these levels include such measures as Tolerable Upper Intake Levels and, for toxic substances, the Reference Dose. These are discrete values with generous safety margins.

By contrast, risk-based approaches evaluate the probability and consequences across the entire range of exposure and seek the lowest risk for the population being considered. For some substances, there is a generous safe range of consumption. For other substances, as illustrated in Figure 4-3, no level of consumption may be completely safe. Using the information depicted in Figure 4-3 would lead to a different recommendation than would be obtained using a traditional safety approach.

### **Closing Remarks**

The consumption of many foods and nutrients is associated with multiple risks and benefits. By applying analyses that integrate multiple risks



**FIGURE 4-3** Hypothetical graph depicting the expected loss from competing risks, individually and combined. This graph could apply to a substance that poses a risk of adverse health effects if intake is low and of toxic effects if intake is high.

SOURCE: Richard A. Forshee, Center for Food, Nutrition, and Agriculture Policy, University of Maryland.

and benefits, one can improve approaches to regulatory policy, dietary guidance, and the public health.

## DISCUSSION

*Moderator: Karl R. Matthews*

Any risk assessment involves a challenge in balancing the need for a parsimonious model that can be explained readily against a comprehensive model that includes all the possible risks and alternatives. It was noted, for example, that changing the intake of one dietary component is likely to change the intake of other components as well; a model that did not take this into account might be simpler but less informative. As another example, focusing solely on *V. parahaemolyticus* in oysters may be insufficient if there is also a risk of norovirus infection. Dr. Forshee mentioned Einstein's view that one's model needs to be as simple as possible but as complex as necessary to address the question.

# Potential Associations Between Foodborne and Chronic Diseases

*Moderator: J. Glenn Morris, Jr.*

This session of the workshop covered a wide array of topics. Initially, three Iranian speakers—Razieh Yazdanparast, Narges Zali, and Ali G. Moltagh—described studies investigating cancer in Iran that included considerable use of genetic techniques. Volker Mai then discussed a study of intestinal microbiota, including ways in which the microbiota might be affected by environmental factors and ways in which they might affect health. Lu Wang provided a description of the National Institute of Health's Human Microbiome Project and indicated that a wealth of new information on microbiota may soon emerge.<sup>1</sup> The session ended with a lively discussion focused mainly on intestinal microbiota.

## SIGNALING PATHWAYS INVOLVED IN CANCER

*Presenter: Razieh Yazdanparast<sup>2</sup>*

This presentation focused on the biological effects of 3-hydrogenkwadaphnin (3-HK). This substance is derived from *Dendrostellera lessertii*,

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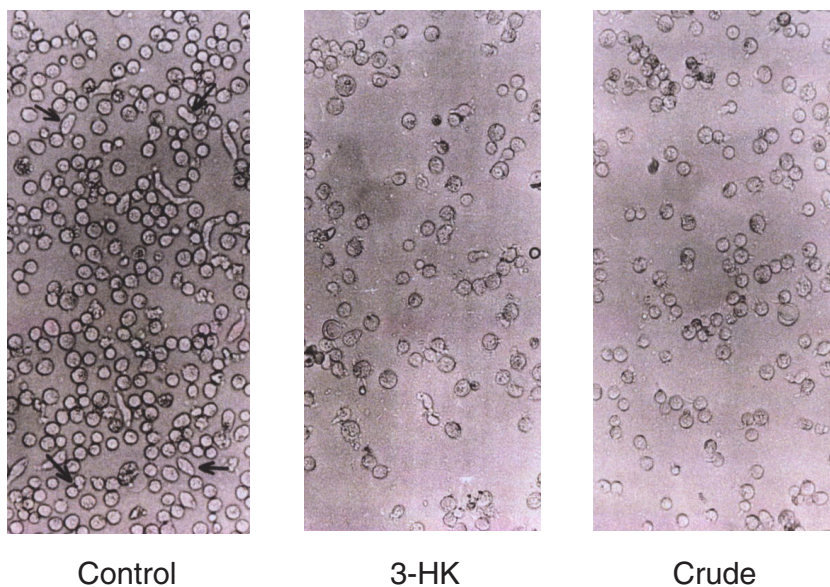
<sup>1</sup>The workshop planning committee, in consultation with Iranian counterparts and other participants, extended the scope of the workshop to include recent research findings in the area of cancer and in potential relationships of gastrointestinal microbiota with chronic disease. Both topics were viewed as important areas of research of mutual interest.

<sup>2</sup>Yazdanparast acknowledged financial support from the Research Council of the University of Tehran, the Research Council of the Ministry of Health, and the Research Council of the National Research Center for Genetic Engineering and Biotechnology. She also acknowledged the assistance of H. Fasehei, M. Abdolmohammadi, H. Sadeghi, M. Mianabadi, A. Sadeghirizi, A. Meshkini, and M. A. Moosavi.

a member of the Thymelaeaceae family of Iranian medicinal plants. The presentation also covered signaling pathways involved in 3-HK-induced apoptosis and in the differentiation of the U937 human leukemic cell line.

Yazdanparast showed a series of slides that demonstrated the anti-proliferative activity of the plant. In one study, for example, the researchers induced breast tumors in rats, treated them with a daily dose of the crude extract, and found substantial tumor suppression. When they evaluated the biological activity of 3-HK versus that of the crude extract with a battery of cell lines, they found that the effects of the chemical and of the crude extract were similar (see Figure 5-1). Importantly, they found that the effect of 3-HK was irreversible and that it showed its effect on proliferating cells but not on resting cells. The latter finding led the researchers to investigate the signaling pathways that are influenced by 3-HK.

Yazdanparast showed a number of slides that illustrated the results of studies concerning the cause of the cell death and distinguishing between adherent cells and suspended cells. The U937 cell line reacted in two different ways to 3-HK: some of the cells went to apoptosis, and some of



**FIGURE 5-1** Effects of 3-hydrogenkwadaphnin (3-HK) and crude extract from *Dendrostellera lessertii* on cell proliferation.

SOURCE: R. Yazdanparast, University of Tehran.

them were guided to differentiation. Further investigations supported the finding that 3-HK has the ability to affect the cells in both ways.

Additional slides illustrated how specific inhibitors blocked the activity of JNK and P38. One conclusion from the studies is that JNK and P38 are involved in apoptosis, which occurs through the FAS/mitochondrial signaling pathway and includes P21 cleavage. Another conclusion is that differentiation involves extracellular signal-regulated kinase (ERK), but caspase is not involved, and P21 is up-regulated rather than cleaved. Yazdanparast is currently involved in studies concerned with how 3-HK works among the apoptotic and differentiating cells with respect to signaling elements, focusing on the fate of P21. She expects that this work will lead to the use of 3-HK as an anti-proliferative drug in the treatment of leukemia.

## MOLECULAR AND GENETIC ASPECTS OF COLORECTAL CANCER

*Presenter: Narges Zali<sup>3</sup>*

In her presentation, Narges Zali briefly described her research on the molecular and genetic aspects of detection of two forms of colorectal cancer: hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP). By providing a number of definitions throughout her talk, Zali helped the audience become more familiar with the molecular and genetic approaches to understanding diseases that were discussed during the workshop.

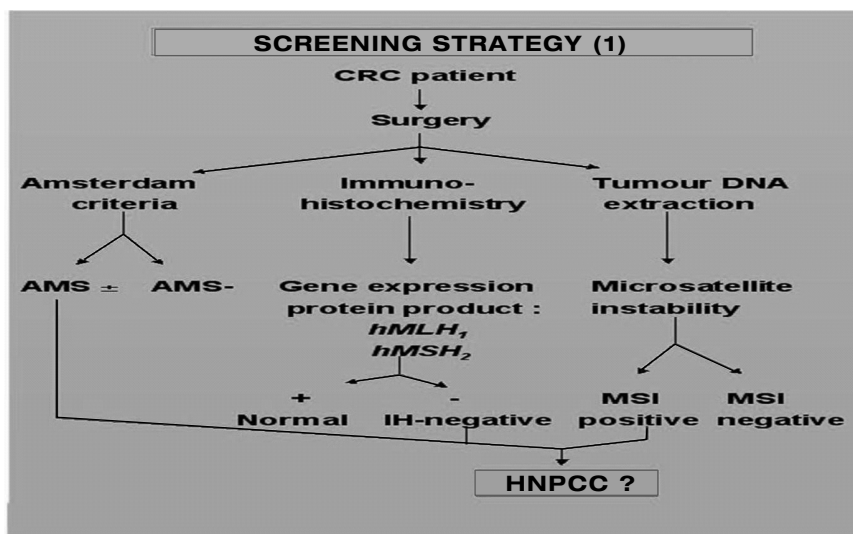
### Hereditary Nonpolyposis Colorectal Cancer

HNPCC is an inherited form of cancer that affects primarily the colon and rectum. It is an autosomal dominant cancer-susceptibility syndrome—that is, a copy of the altered gene inherited from either parent is enough to increase cancer risk—for which the gene map locus is on chromosome 2, short arm, band 22 to 21. It is associated with germ line mutations in mismatch repair (MMR) genes. MMR proteins repair problems that arise during DNA replication, and mutations in the MMR genes damage the body's ability to repair the mistakes made during DNA replication, leading to an increased risk of cancer.

For the study that Narges Zali described, all colorectal cancer patients

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<sup>3</sup>Narges Zali expressed thanks to the National Academy for Educational Development, especially to Beverly Attallah, and to the National Academies for the opportunity to present her work.



**FIGURE 5-2** Genetic tests for the detection of hereditary nonpolyposis colorectal cancer (HNPCC). IH-negative stands for immunohistochemistry-negative and means that a specific gene was not expressed.

SOURCE: N. Zali, Shaheed Beheshti University of Medical Sciences.

from the hospital-based cancer registry at the Research Center for Gastroenterology and Liver Diseases were asked to enroll. After receiving the patients' informed consent for the procedures and for genetic counseling, staff collected blood samples and paraffin-embedded blocks of tumoral tissue that were obtained during surgery. The research team extracted genomic DNA from blood and tissue and ran a series of genetic tests for HNPCC, as shown in Figure 5-2.

To help clarify the screening strategy, Narges Zali explained some of the terms used and showed slides illustrating the findings. Immunohistochemistry (IHC) is a technique to detect the presence of a particular protein in a tissue sample through the use of antibodies to that protein. With IHC, one can analyze the expression of MMR genes by looking for their products, the various MMR proteins.

MSI occurs when microsatellites (stretches of short, repeated sequences of DNA) vary in length in an individual. MSI indicates errors occurred in the DNA replication process and thus a deficiency in the MMR repair function. Two techniques are available for the detection of MSIs: (1) the older gel electrophoresis, and (2) the newer and more sensitive fragment analysis.



If the IHC finds that a specific gene is not expressed, the next step is microsatellite instability (MSI) analysis for that gene and then a search for mutations. If the IHC result is normal and Amsterdam criteria<sup>4</sup> are positive, the next test on the tumor tissue is for MSI, potentially followed by a genetic analysis of the MMR genes.

If the patient has a positive high MSI, the next step is to sequence and search for MMR genes (not shown in the figure) using a polymerase chain reaction (PCR). To date, the researchers have found 20 MMR germ line mutations in 18 out of 47 families with colorectal cancer. They have also found several novel mutations.

### **Familial Adenomatous Polyposis**

The research group is also working to determine the molecular epidemiology of APC/MYH genes among Iranian patients with familial adenomatous polyposis (FAP). The group uses a clinical-molecular approach in the genetic testing of patients with FAP. If examination of the family tree indicates that the condition is familial, PCR and sequencing are used to determine whether there are point mutations. If such mutations are found, the clinician refers the patient for a colonoscopy and for follow up. For cases in which these mutations are not found, the research group is investigating a new technique called multiplex ligation-dependent probe amplification to search for large deletions in the tumor-suppression gene APC.

## **SCREENING OF HIGH-RISK POPULATIONS FOR COLORECTAL CANCER IN IRAN**

*Presenter: Ali G. Motlagh*

Motlagh provided background information about colorectal cancer in Iran, briefly described molecular events that are associated with the development of colorectal cancer, discussed the development of technology in Iran to detect the genetic mutations that lead to colorectal cancer, and suggested useful next steps.

### **Background Information**

In Iran, colorectal cancer is the third most common cancer among women and the fourth most common cancer among men. Sixty-five per-

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<sup>4</sup>Amsterdam criteria are used to identify families that are likely to have hereditary non-polyposis colorectal cancer.



cent of the colorectal cancer in Iran is estimated to be sporadic, 25 percent familial, 4 percent hereditary nonpolyposis colorectal cancer (HNPCC), 1 percent familial adenomatous polyposis (FAP), and 5 percent other. Genetics and the environment both play a role in the development of colorectal cancer, but the particular roles vary according to the type of cancer. In particular, genetic factors are known to play different roles in different types of colorectal cancer. In sporadic types, for instance, low-penetrance genes are more important than high-penetrance genes, while the opposite is true for familial cases.

### **Molecular Events Associated with Colorectal Carcinogenesis**

Two pathways are known to be important in colorectal carcinogenesis: the chromosomal instability pathway and the microsatellite instability (MSI) pathway. It has been proposed that MSIs result from a deficient mismatch repair (MMR) system. MSIs are found in the major tumors of patients with HNPCC as well as in 15 percent of sporadic colorectal cancers.

Three methods exist for studying alterations of the MMR mechanism: sequencing the involved gene, detection of gene products, and MSI analysis. Motlagh pointed out that testing for MSI is a powerful method to screen for HNPCC and that the finding of MSIs in sporadic tumors suggests a more favorable prognosis although the response to chemotherapy is uncertain.

A person with two or more relatives who have developed colorectal cancer has a substantially higher risk of developing colorectal cancer himself or herself, and the cancer may occur at a relatively young age. Clinical criteria that include family history and the patient's cancer history are helpful in identifying those persons who are good candidates for genetic testing.

### **A Project to Develop Technology for the Detection of Genetic Mutation for Colorectal Cancer in Iran**

Motlagh described a project in Iran aimed at developing and using technologies for detecting the genetic mutations leading to colorectal cancer and at establishing a genetic counseling service for high-risk populations. The project will also establish a gastrointestinal cancer registry database, develop IHC and MSI techniques, and create other genetic-analysis capabilities.

Records were reviewed for 600 patients with colorectal cancer from 8 of the 30 provinces of Iran. Software was specially designed for collecting the data, and the data were added to the cancer registry database. Inves-

tigators obtained additional data in order to be able to perform survival analysis, and they traced pedigrees backward and laterally. Amsterdam II criteria were used to identify HNPCC, and Bethesda guidelines were used in identifying HNPCC-related neoplasms.

The investigators conducted various genetic tests and found that most mutations were in MLH1 (a gene that codes for a membrane protein), which is similar to findings from China, Korea, Finland, Sweden, and Spain. The phenotype features that the researchers found may have value in the design of genotype-specific screening.

### Future Considerations

Since colorectal cancer is triggered by interactions of genes with the environment, and since environments differ around the world, achieving a consensus on screening guidelines may be difficult. Based on the most recent update of the non-colorectal, non-neuroendocrine guideline and on recent trials, Motlagh and colleagues suggested that the optimal method for screening a high-risk population for colorectal cancer would include

- patient evaluation with Bethesda guidelines;
- MSI analysis and IHC testing for MMR protein;
- mutation analysis and patient evaluation with Amsterdam guidelines; and
- hypermethylation of MHL1 and BRAF<sup>5</sup> mutation analysis.

Because this method would probably not be cost effective, the Iranian group has mapped out the following three-phase effort to refine and make effective a screening method for the Iranian population by using a small sample of patients:

1. Estimate the accuracy of IHC and MSI analysis for the prediction of the MMR mutation, design a computer model for predicting the MMR mutation, conduct a cost-effectiveness analysis to identify the most suitable screening guidelines for the Iranian population, and search for the best method to distinguish familial colorectal cancer from HNPCC.
2. Conduct a pilot study of a population at high risk for colorectal cancer in Tehran province using colonoscopy and laboratory tests, and estimate the accuracy of these tests for screening the Iranian population for colorectal cancer.
3. Develop a comprehensive program for risk stratification and risk modification among those at high risk for colorectal cancer.

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<sup>5</sup> BRAF is a protein that plays a central role in the growth and survival of cancer cells.

## DIET, MICROBIOTA, AND CARCINOGENESIS

*Presenter: Volker Mai*

Mai provided background information about the intestinal microbiota and its investigation, briefly described some studies in which he has been involved, listed desirable characteristics of future studies, and gave a few closing remarks.

### Overview

#### *Description of the Intestinal Microbiota*

The intestinal microbiota could be considered an organ. It consists of approximately  $10^{11}$  to  $10^{12}$  bacterial cells per gram of stool. This means that humans have 10 times more cells in the form of bacteria than they have human cells. The gut microbiota has three key functions:

- 1) *Metabolic*: Examples include the fermentation of non-digestible dietary residue and endogenous mucus, salvage of energy as short-chain fatty acids, production of vitamin K, and the absorption of ions.
- 2) *Trophic*: This involves development and homeostasis of the immune system and the control of epithelial cell proliferation and differentiation.
- 3) *Protective*: Bacteria may prevent the attachment of pathogens in the intestines and thus reduce the risk of disease.

#### *The Study of the Intestinal Microbiota*

Studying the gut microbiota is difficult for a number of reasons. There is no efficient way to sample from the proximate colon without an initial cleansing, for example. Mai said that both the lumen material and the bacteria that attach to the epithelium are needed to study the gut microbiota, but that this situation poses challenges. For example, formalin, which is used to preserve biopsy samples, depletes the mucus layer. Furthermore, the proportion of organisms that can be cultured is very low, there are difficulties in speciating bacteria, and the work is very labor intensive. Recently, molecular analysis methods have opened new avenues in the study of gut microflora.

Interactions between diet and the microbiota might distort epidemiological observations. For example, if flora associated with a low risk of certain diseases colonize the intestine, they may efficiently ferment fiber to create such beneficial end products as butyrate. By contrast, if flora associated with a high risk of those diseases colonize the intestine, they may not ferment the dietary fiber. The movement of intact fiber through

the colon, in turn, might deplete the mucus and increase the risk of a chronic infection. Mai concluded that studying these complex interactions requires multidisciplinary research involving microbiologists, immunologists, epidemiologists, and others.

### Ongoing Studies

In Mai's laboratory at the University of Florida in Gainesville, the methods of studying the intestinal microbiota range from the use of denaturing gradient gel electrophoresis to microarrays. The group is using a "shotgun" method that involves collecting stool, extracting DNA, performing PCR tests, subcloning, and sequencing. This method should allow the detection of all bacterial species that are present at a concentration of more than  $10^7$  bacteria per gram of stool.

Cancer mortality data show a number of similarities between the United States and Iran. In both countries, for instance, colorectal cancer is the third-leading cause of cancer deaths for both men and women. In the United States, African Americans of both sexes experience higher incidences and higher mortality rates from colorectal cancer than do whites. For this reason, Mai's group is especially interested in studying the risk of colorectal cancer and the potential contributions of environmental factors to colorectal carcinogenesis among African Americans.

If one is interested in preventing cancer, then focusing on environmental factors means focusing on those factors that can be changed in order to reduce risk. Current evidence suggests that higher intakes of folate, calcium, vitamin D, vegetables, and perhaps fiber might reduce the risk for colorectal cancer. In contrast, the risks for colorectal cancer appear to be increased by a high body mass index and by the consumption of the nitrosamines in processed meat and the heterocyclic amines in grilled meat. Mai's laboratory has the long-term goal of developing interventions that modify the intestinal microbiota toward a healthier composition, but he noted that he is aware that dietary factors have not yet been convincingly associated with cancer risk.

#### *Diet, Microbiota, and the Prevention of Intestinal Adenomas in $Apc^{Min}$ Mice*

Mai briefly described a study that looked at the question of whether diet might affect the gut microbiota and, in turn, affect the development of cancer in the intestinal tract. The study used  $Apc^{Min}$  mice, which are a standard mouse for studies of human colorectal carcinogenesis. The mice have a genetic predisposition to developing intestinal adenomas at an early age. The mice were divided into groups including a high-risk-diet group, a low-risk-diet group, and a set of controls, all of which were fed

ad libitum, plus another group that was fed the control diet but with a 40 percent calorie restriction. The researchers found that both the low-risk diet and the calorie-restricted diet reduced the number of polyps in the mice significantly, but the reductions occurred via different pathways. The full results of the study suggest that specific dietary interventions reduce intestinal carcinogenesis, that diet strongly affects the intestinal microbiota composition, that some bacteria appear to be associated with lower risk, and that diet and microbiota likely affect immune function. Mai provided detailed information to the workshop attendees by distributing his paper "Intestinal microbiota: A potential diet-responsive prevention target in *Apc*<sup>Min</sup> mice" (Mai et al., 2006).

### *Diet and Microbiota Studies in Humans*

Mai has conducted a pilot study of 52 African Americans and 46 Caucasians to look for associations between diet and microbiota and to explore differences in the microbiota between people in the two groups. One interesting finding was an association between dietary fiber intake and higher amounts of lactic acid bacteria (which are generally thought to be beneficial). African Americans had twice as many *Bacteroides* as did the Caucasians.

An ongoing colonoscopy screening study may offer an opportunity for developing collaborations with the Iranians. In this study investigators are measuring diet, collecting stool samples, recording normal status, and collecting biopsy samples from subjects with the aim of determining if specific parts of the gut microbiota are associated with colorectal cancer risk.

### **Desirable Characteristics of Future Studies**

Several features will be important in future studies of the human intestinal and fecal microbiota:

- An understanding of the standard dynamic of the microbiota needs to be developed because epidemiological studies require assurance that a sample collected at a specific time really is representative of the microbiota over time.
- The use of multiple time points would help clarify dynamics.
- Larger studies are needed; to date studies have involved fewer than 10 people.
- Studies of different populations would provide valuable information on variation.

- Studies of interventions are needed to determine the potential for modification of the microbiota.
- Standardized methods are needed so that comparisons can be made between studies.

### **Closing Remarks**

In closing, Mai highlighted the following points:

- Gut microbiota contribute substantially to intestinal physiology and thus likely to human health.
- The complexity of the gut microbiota and its metabolic abilities and dynamics are not yet fully understood.
- Microbiota composition is affected by diet. Specific bacteria appear to be associated with carcinogenesis.
- Future studies need to test specific hypotheses rigorously.

### **HUMAN MICROBIOME PROJECT**

*Presenter: Lu Wang*

The Human Microbiome Project is a U.S. National Institutes of Health (NIH) Roadmap project. Roadmap projects have been characterized as high-risk and potentially high-return projects. The Human Microbiome Project has been funded at a level of slightly more than \$100 million for a 5-year period. In his presentation, Lu Wang briefly described the project and listed its initiatives.

### **Overview**

The human microbiome is the collection of genomes of all the microbes that inhabit the human body. Several hundred distinct phyla of microbes live in the human body. As mentioned previously by Mai, the human microbiota is thought to have a profound influence on human health via various effects that it has on human physiology and nutrition, immunity, and development.

Current evidence indicates that the human microbiome has different patterns at different anatomical sites. New sequencing technology makes it possible to analyze the genomic content of a human microbiome. The publication *The New Science of Metagenomics: Revealing the Secrets of Our Microbial Planet* provides a useful perspective on this type of research (NRC, 2007).

The goal of the Human Microbiome Project is to characterize the microbes that inhabit the human body and to examine whether changes in the microbiome can be correlated with disease. In fiscal year 2008, the NIH will award cooperative agreements and grants to support the project. The project's policy will be to release immediately the data it collects and the resources it develops.

The project will address the following questions:

- Is there a core microbiome? There is currently a wide divergence of opinions on this matter.
- How much variation in the microbiome is there among individuals? Answering this question may require taking into account the various environments to which people are exposed.
- Can changes in microbial populations be connected with factors such as disease, age, diet, antibiotics, and sex?
- Can information about an individual's microbiome be demonstrated to offer any diagnostic or therapeutic benefits?

### **Initiatives of the Human Microbiome Project**

A broadly based working group of the NIH identified the following seven initiatives that the Human Microbiome Project will support:

1. Developing a reference set of microbial genome sequences and a preliminary characterization of the human microbiome, with a focus on healthy individuals
2. Investigating relationships between changes in the human microbiome and disease
3. Developing new microbial genomics technologies
4. Developing new tools for the computational analysis of specific types of data
5. Establishing a data analysis and coordinating center with functions related to tracking, storage, and distribution of data, coordination of data analyses, the development of data-retrieval tools, coordination of standard development, and establishing a mechanism to display project activities
6. Establishing a central, reasonably priced resource for materials, reagents, cultured organisms, etc.
7. Addressing ethical, legal, and social implications of Human Microbiome Project research, covering topics such as clinical and health implications, forensic uses of microbiome profiles, bioterrorism and bio-defense applications, and privacy issues

### Closing Remarks

The group that is responsible for implementing the Human Microbiome Project includes four institute directors and representatives from all 27 NIH institutes. The website <http://nihroadmap.nih.gov/hmp/> provides further information about the NIH Roadmap Human Microbiome Project and also posts announcements about new requests for applications.

### DISCUSSION

*Moderator: J. Glenn Morris, Jr.*

The participants spent considerable time discussing studies of the intestinal microbiota and their possible relationship with the development of disease. It was emphasized that this is an exciting new field made possible by technological advances and that the development of new genetic capabilities is leading to major changes in the concept of microbiology. Because the field is very new, there are many questions for which definitive answers are not yet available. Topics that sparked special interest include the relationships of the microbiota to the development of chronic disease and the ways that this might be studied, the effects of various factors on the microbiota in the intestinal lumen, the identification of organisms that make up the microbiota, and potential future studies.

#### Relationships of the Microbiota to the Development of Chronic Disease

Epidemiological evidence indicates that rates of colorectal cancer are much lower in Africa and in some other parts of the developing world than they are in the industrialized countries. Mohammad Reza Zali noted that food in the developing countries tends to contain more bacteria than food in industrialized countries, which could lead the residents of developing countries to have higher numbers of bacteria in their intestinal tracts than do residents of industrialized countries. It also was noted that rates of colon cancer increase when people move to more industrialized countries.

Mai explained that it is much more difficult to study the relationships of microbiota in the intestinal lumen with the development of colorectal cancer or with other chronic diseases than it was to study *Helicobacter* and its association with disease. The stomach environment is essentially sterile, except for the presence of *Helicobacter* itself, which made it relatively easy to isolate and identify the bacterium. The intestines, by contrast, have a population of microorganisms that is vastly more complex.



It is possible that shifts in the proportions of various microbial groups are related to changes in disease risk. Because the studies of the intestinal microbiota conducted by Mai's group have so far involved subjects undergoing screening colonoscopies rather than patients with cancer, however, his group has not yet been able to show any associations between the microbiota and colon cancer.

### **Effects of Various Factors on the Microbiota in the Intestinal Lumen**

#### *Cleansing and Antibiotics*

The preparation of the colon for a colonoscopy has a major effect on the bacteria that can be obtained in a biopsy sample. The bacteria that have the ability to attach to the inner mucus layer and thus remain in the colon may be completely irrelevant to health risks. For this reason, fecal samples may be more useful to a study of the microbiota than are biopsy samples. If it were possible to sample the intestinal contents of a corpse right after a person's death, one could compare the composition of the microbiota at different parts of the intestine. Clearly, the study of the intestinal microbiota is complicated by the difficulty of obtaining samples from the proximal intestine.

It is not clear what effect antibiotics have on the overall composition of the microbiota over time, and the findings will depend in part on the sensitivity of the technique used. Mai suggested that antibiotics have a smaller effect on the intestinal microflora than does colonoscopy.

#### *Dietary Change*

The period of time required to stabilize the microbiota after a drastic dietary change (such as a change from omnivore to vegetarian or the addition of a probiotic substance to one's diet) has not been studied well. Initial studies suggest that about seven days may be required for the microbial composition to stabilize after it has been seriously disrupted. When the substrate in the intestines changes, the bacteria that are best adapted to use the substrate gain energy and appear to dominate rather quickly. Depending on which bacteria are present in high proportions, the concentrations of compounds present in the intestinal lumen change, and this may influence susceptibility to cancer. It is an extremely complex system, and its investigation has only recently begun to receive support from the NIH.

Some participants expressed interest in studying the effects that malnutrition has on the composition of the microbiota and how those changes might affect the immune system, potentially resulting in adverse health outcomes.

### **Identification of Organisms That Make Up the Microbiota**

A very large percentage of the microorganisms populating the intestine cannot be cultured. Thus the study of the microbiota now generally involves extracting DNA from a stool sample and identifying both anaerobes and aerobes using genetic techniques. The genetic studies have raised questions about the concept of bacterial species. There is much genetic exchange, and the relationship of different molecular signatures to different bacteria is not completely clear. Morris indicated that a tremendous revolution is just beginning to occur in our understanding of the composition of microflora of the human gastrointestinal tract.

Although Mai focused his discussion on the potential role of bacteria in the development of colorectal cancer, his group has not ruled out a potential role for yeasts. However, because the number of yeasts per person is much smaller than the number of bacteria (on the order of  $10^5$  or  $10^6$  for yeast, compared with  $10^{11}$  or  $10^{12}$  for bacteria), few yeasts are found in microscopic studies of the gut microflora. Special methods will be needed to study the involvement of yeasts.

### **Future Directions**

The evidence suggests that very complex metabolic and biochemical reactions are occurring continually within our intestines and that disturbances of the microbiota might substantially change a person's ability to handle specific toxins, metabolic by-products, or other substances in the intestine. This subject lies within the intersection of foodborne disease, the bacteria in the intestines, and the occurrence of chronic disease. Morris said that there is a need to conduct studies in locations outside the United States in order to understand the differences that may arise in different geographic areas. Considering the development that Iran is undergoing, Mai suggested that it could be a promising region for the study of a variety of factors that affect the risk of developing colorectal cancer. Such study also would have the benefit of helping identify the environmental causes of cancer that could be controlled.

# 6

## Approaches to Health Education

*Moderator: Ali Ardalan*

**D**uring this session, participants learned about three very different approaches to health education. First, Keith Yamamoto outlined the vision for integrated medical research training at the University of California at San Francisco; then Mohammad Reza Zali described the medical education approach now being used in Iran; and, at the conclusion of the meeting, Ali Ardalan used the Internet to familiarize the group with an open source Internet library called Supercourse—a resource that is available around the world.

### **INTEGRATED MEDICAL RESEARCH TRAINING AT THE UNIVERSITY OF CALIFORNIA**

*Presenter: Keith Yamamoto*

Describing the integrated medical research training at the University of California as a work in progress, Yamamoto focused on the vision that the University of California at San Francisco has for integrating health science training with research. He suggested that institutions that enhance the opportunities for physicians and Ph.D. researchers to interact productively will be rewarded by achieving new levels of excellence. Once he had introduced the topic, Yamamoto described four new programs that are underway at the university and then finished with a few closing remarks.

## Introduction

Academic medical centers have four core missions and responsibilities: education, research, patient care, and community outreach. At the University of California at San Francisco, all four are carried out simultaneously, and, considered as individual efforts, each has been excellent.

In 2002, however, a closer look revealed a medical curriculum that was very conventional. Science courses, for example, were neither connected with each other nor with the practice of medicine; and the departmental residency programs were focused on the specialty needs of the department.

On the other hand, for many years the doctoral programs and organized research units had taken the form of umbrella programs (large programs that crossed department lines, and, in some cases, crossed school boundaries). The Cardiovascular Research Institute, for example, was trans-departmental, dealing with clinical medicine as well as basic science. The question arose, then, "Can the four core missions be integrated better?" The university's response, as summarized by Yamamoto, is given below.

## Integrative Changes Being Made

The integrative changes involve four new programs:

1. A new medical curriculum
2. The Clinical and Translational<sup>1</sup> Science Institute
3. The Program in Quantitative Biology
4. The Institute for Molecular Medicine and the Graduate Program in Molecular Medicine

### *Medical Curriculum*

The new medical curriculum integrates basic, clinical, and social and behavioral sciences throughout the medical school's four-year course of study. Students often work in small groups, and their instruction emphasizes problem solving and the relationships between research and clinical outcomes. The elective Pathways to Discovery feature of the program is designed to create a culture of inquiry, innovation, and discovery that will benefit all medical trainees. Pathways to Discovery brings together medical students and residents across department boundaries. Each of the pathways includes courses, research, and mentoring; and each pathway

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<sup>1</sup>"Translational" refers to finding applications of scientific discoveries in patient care.

leads to a certificate or, in some cases, a master's degree. In the future, some of the pathways may lead to a doctoral degree, Yamamoto said.

### *Clinical and Translational Science Institute*

The goal of the Clinical and Translational Science Institute is to accelerate the pace of translation of scientific discovery into patient care. The National Institutes of Health Roadmap provided the funding for this institute (more than \$100 million for 5 years) through its Clinical and Translational Science Awards program. More than 200 faculty members have been involved in designing 14 programs that will promote translation by creating or integrating services, resources, and policies in the following five separate areas:

1. Education
2. Basic, translational, and clinical research
3. Clinical trials
4. Corporate alliances (locally, nationally, and globally)
5. Community interactions

### *Program in Quantitative Biology*

This graduate program in biomedical research was designed to attract faculty and students from the physical sciences, mathematics, computation, and engineering. These disciplines are now all well represented in the resulting umbrella program. Previously, such representation was absent. Yamamoto indicated that the program has led to changes in the nature of research and in the way it is conducted—no matter whether that research is basic, translational, or clinical.

### *Institute for Molecular Medicine*

The Institute for Molecular Medicine offers an umbrella program for medical trainees. A consortium of the university's medical departments oversees joint faculty recruitment and space allocation and administers the M.D./Ph.D. program, the molecular medicine residency/fellowship program, and the Graduate Program in Molecular Medicine.

The Graduate Program in Molecular Medicine serves as a point of access into the Institute for Molecular Medicine—a portal of entry that is available to graduate students in any doctoral program. The program offers seminars, symposia, and intensive mini-courses that focus on the mechanisms of disease and that range from basic principles to patient care. Because the program offerings are designed to attract graduate

students, fellows, medical students, residents, and faculty, the learning opportunities serve a key integrative function. Discussions among participants from different educational and experiential backgrounds may lead to the discovery of a range of approaches and opportunities. A person may choose to attend formally, with the goal of qualifying for a certificate, or informally. A student in the pharmacology program might, for example, decide to spend two weeks learning about Alzheimer's disease from experts.

### **Closing Remarks**

Academic medical centers have an opportunity to find new levels of integration that will lead to new levels of excellence. Yamamoto expects that the new opportunities generated by improved integration will lead to new discoveries and will speed the course of discoveries in basic sciences and in the translational and clinical areas.

## **HEALTH EDUCATION IN IRAN**

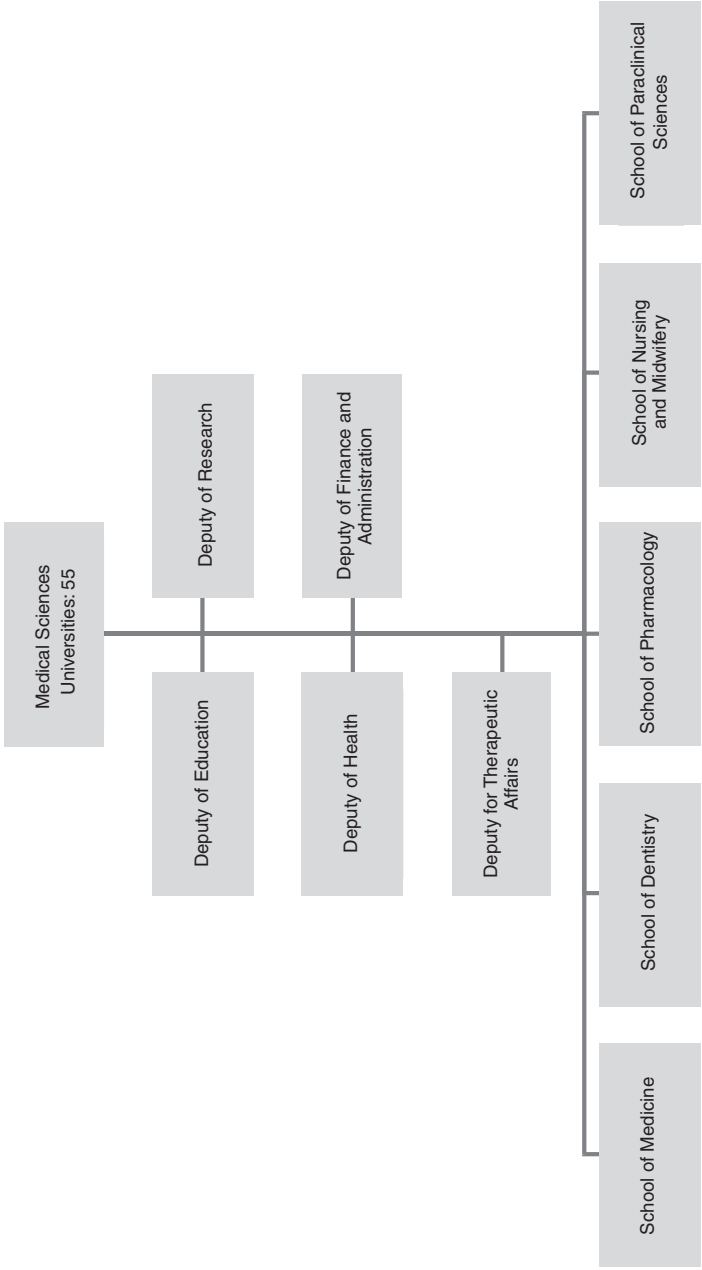
*Presenter: Mohammad Reza Zali*

With the establishment of a primary health care system throughout Iran during the period from 1980 to 2003, life expectancy increased dramatically, maternal and infant mortality decreased dramatically, and the rate of population growth slowed substantially. Now Iran's population has a large percentage of young people and also a growing number of the elderly. The population is also gradually becoming more urban. The major causes of mortality in 2003 were cardiovascular disease, cancer, and accidents. All of these factors are relevant to the future needs for health care services and medical education in Iran.

In his presentation, Zali briefly described the relationship of the Iranian health care system to the medical science universities. Then he provided an overview of medical education and a description of curricular reform in undergraduate medical education.

### **Relationship of the Health Care System to Medical Education**

The Ministry of Health and Medical Education oversees both the health care system and medical education, as mentioned in Chapter 2. Figure 6-1 gives the organization of the Medical Sciences Universities. The Deputy of Health oversees the teaching hospitals as well as the state, urban, and rural health network described in Chapter 2.



**FIGURE 6-1** Iran's Medical Sciences Universities organizational chart.  
**SOURCE:** M. Zali, Shaheed Beheshti University of Medical Sciences.

## **Overview of Medical Education**

The curriculum for medical education is standardized across the Iranian medical schools. In a seven-year program, the first two years are spent in the basic sciences, and the third year covers pathophysiology and the study of the signs and symptoms of disease. Subsequent years are focused on the externship and internship.

Iran has 28 medical schools in the public sector, 5 in the armed forces, and 22 in the private sector. Of the 1,600 medical students enrolled each year, more than 50 percent are female.

The providers of health care in Iran must deal with the needs of a growing young population who face problems related to addiction, violence, accidents, and communicable diseases. They also must deal with the needs of a growing elderly population struggling with diabetes, cardiovascular disease, obesity, cancer, Alzheimer's disease, and other ailments. To address these challenges, Iran recognizes the importance of developing its human resources and taking appropriate actions, particularly in the following three areas:

1. Improvements in medical education, including the revision of medical curricula
2. The training of a new generation of medical researchers
3. Increases in the amount of patient-oriented and disease-oriented research, including both basic and clinical research

Notably, biomedical research citations from Iran have increased sharply since about the year 2000.

## **Curricular Reform in Undergraduate Medical Education**

In an effort to help improve medical education in Iran, the University of Shaheed Beheshti undertook a pilot study on the reform of medical school curricula. The proposed curriculum reform would take an integrated approach, with case-based study; the opportunity for students to enroll in either science or public health research; and an opportunity for students to become familiar with a scientific career.

The developers of the Iranian curriculum reform plan attempted to be comprehensive in their approach. The reform is to be based on the best available evidence, using a formal process of option appraisal. This process produces the "evidence-based" content that is mentioned below. The resulting curriculum must be in accord with international and national standards. The effort began in 1999 with a needs assessment. This was followed by an extensive series of curriculum-development activities undertaken by a broadly interdisciplinary team. The proposed plan required

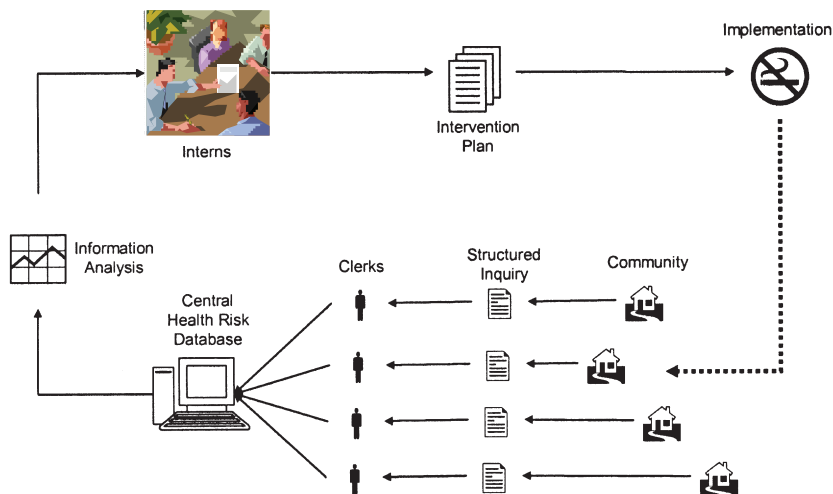


and obtained approvals from a number of officials, including the Minister of Health.

The pilot study was implemented beginning in 2004 with such steps as the development of new courses, the writing of textbooks, operational planning, and capacity building. Emphasis was placed on evidence-based content. Interdisciplinary, curriculum, and steering committees were assembled to provide input and direction. The resulting new curriculum vertically integrates clinical content with the study of organ systems. Courses include lecture-based courses, self-directed reading modules, small study-group modules, project modules, and laboratory-work modules. One very important aspect of the reform is getting the students involved in community health care. Figure 6-2 illustrates a typical flow of activities that could take place when interns work in the community.

Mohammad Reza Zali emphasized the key role played by specially trained clinical preceptors. They work with medical students in supervised learning facilities, skill laboratories, and ambulatory clinical training; and they provide guidance about learning portfolios and logbooks, educational prescriptions, and study guides.

The curricular reform program has been undergoing both internal



**FIGURE 6-2** A typical flow of activities when interns are placed in the community.

SOURCE: M. Zali, Shaheed Beheshti University of Medical Sciences.

and external evaluation. Observations, questionnaires, and interviews are used to obtain data on context, input, process, and output. A key aspect of the evaluation is to determine whether the program meets national standards. The preliminary report, which will be released soon, indicates that students have been performing well. In particular, the reformed medical education is resulting in improvements in the knowledge, skill, and awareness of the participants.

### **Closing Remarks**

Mohammad Reza Zali is hopeful that talented students will attract other talented students to research. He quoted from Plato's *The Laws*, written in 490 B.C.: "Good clinical medicine is a marriage of scientific knowledge and human care."

### **SUPERCOURSE—THE GLOBAL HEALTH NETWORK**

*Presenter: Ali Ardalan, with Ronald LaPorte by Telephone*

The last presentation covered Supercourse, the open source Internet library developed under the leadership of Janice Dorman and Ronald LaPorte at the World Health Organization Collaborating Center at the University of Pittsburgh's Graduate School of Public Health. Other developers include Ali Ardalan, Faina Linkov, Mita Lovelekar, Francois Sauer, and Julia Shubuikova. During the presentation, Ardalan connected with the Internet site and projected an assortment of pages on the screen to illustrate the contents and uses of Supercourse. Afterward, LaPorte commented via a telephone connection.

### **Overview**

Supercourse is a global repository of lectures on public health and prevention, which is designed for use by educators across the world. It can be accessed at <http://www.pitt.edu/~super1/>, and the materials on the site may be used at no cost. Supercourse has a network of more than 42,500 scientists in 174 countries who share materials. Together they have created a library of more than 3,232 lectures in 26 languages. As indicated on the website, the Supercourse sometimes is called the Global Health Network University.

The Supercourse offers lectures on epidemiology, surveillance, nutrition, cancer prevention, and a myriad of other topics, identifying each of the authors of those lectures and the dates the lectures were written.

Numerous Nobel Prize winners<sup>2</sup> have contributed lectures to the Supercourse. Many of the lectures have been translated into Chinese, Spanish, Arabic, and other languages. The site includes a number of ways to search for articles, including an option called "New Lectures." Ardalan specifically recommended viewing the lecture called "The Golden Lecture of Prevention."

### **Improving Disaster and Public Health Education Worldwide**

One way to improve disaster education and public health education is to share effective lectures and slide presentations for free. The Supercourse does this. Currently the site holds 250 lectures that deal with preparing for and responding to disasters; they were submitted by experts from 50 countries.

When a health emergency occurs, the Supercourse can play a key role in providing relevant information through its "Just-in-Time Lectures." Within days of an event, experts can develop lectures and disseminate them through the Supercourse network. This occurred, for example, after the 2004 Indian Ocean tsunami. The network recruited 40 global experts, who generated a lecture within 3 days; that lecture was distributed to 120 countries and reached approximately 200,000 students. Another Just-in-Time Lecture dealt with severe acute respiratory syndrome (SARS).

### **Closing Comments**

One goal of the Supercourse is to provide an expert global network and expert content online—useful information that is available in advance of adverse events—thus helping to protect the public health through such measures as the prevention of outbreaks of foodborne illness.

## **DISCUSSION**

*Moderator: Ali Ardalan*

Three major topics were covered during the discussion period: the extent of curricular reform in Iran, aspects of the integration of medical research training that are potentially applicable in both Iran and the United States, and some details about the Supercourse. Highlights appear below.

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<sup>2</sup>Baruch S. Blumberg, Leland H. Hartwell, Eric R. Kandel, Klaus von Klitzing, Joshua Lederberg, Merid Murad, Paul Nurse, Douglas Osherooff, and Rolf R. Zinkernagel (<http://www.pitt.edu/~super1/Nobel/nobels.htm>).

### Curriculum Reform in Iran

The pilot study of the curriculum reform program is being carried out only at Shaheed Beheshti Medical University. If the pilot study shows favorable results after 5 to 10 years, the government will allow other universities to adopt the reformed curriculum.

Organ system-based education, evidence-based education, and a new evaluation system are three of the reform program's main emphases. In the pilot program, the students focus on evidence-based medicine, in part by performing extensive searches of reliable sources on the Internet. Nosratollah Naderi, a preceptor in the program, said that the reform program has been successful in providing students with the knowledge they need to treat their patients and to solve problems.

### Integration of Medical Research Training

#### *Government Approval of Programs*

Participants noted that if the government must approve program changes, as is the case in Iran, it can substantially delay the implementation of plans. Dr. Yamamoto said that the types of changes—such as the establishment of umbrella programs—being made at his university (the University of California) did not require approval by the governing body of the university, but that new degree programs would require approval and thus would require more time to get started.

#### *Certificates Offered by the Graduate Program in Molecular Medicine*

Dr. Yamamoto explained that the certificates offered in the Graduate Program in Molecular Medicine do not yet have intrinsic value, but they may be useful additions to the graduate's curriculum vitae. If the employers who hire the graduates determine that the training has been valuable, the certificates will acquire value.

### Supercourse

Dr. LaPorte of the University of Pittsburgh expressed great appreciation to colleagues in Iran, especially Ali Ardalan, for their invaluable assistance as collaborators on the Supercourse project.

Its courses are translated by volunteers who reportedly like to do this work. One person in Mexico is translating 800 lectures into Spanish. About 140 medical students in China are translating the entire Supercourse into Chinese.

It is possible to identify the most recent lectures on the website, and one can trace changes in the content of lectures on similar topics over time.

Dr. LaPorte closed by repeating a comment made by the head of Internet technology at the U.S. National Aeronautics and Space Administration—that it is better to have an expert global network and expert content available before a food-associated outbreak occurs than to accumulate the information afterward.

# Opportunities for Future Collaboration

*Moderators: Michael Doyle and Mohammad Reza Zali*

During the final session of the workshop, all the participants were invited to share their views concerning possible topics for future workshops and concerning opportunities for future collaboration.<sup>1</sup> As a part of the discussion, U.S. participants suggested some potentially fruitful contacts that the Iranians might make during their remaining two weeks in the United States. The text below summarizes points made during the discussion. No decisions were made by the participants.

## JOINT WORKSHOP TOPICS

Potential topics that were mentioned for future Iranian–U.S. workshops include the following:

- Applying lessons learned from the surveillance pilot project carried out near Damovand to help strengthen the Iranian surveillance system
- Using experiences from Iranian and American foodborne surveillance systems to develop intervention programs to prevent foodborne illness
- Expanding the topic of foodborne disease to include the role of bacteria in chronic diseases such as cancer and inflammatory bowel disease,

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<sup>1</sup>To provide context for some of the points made during the session, the reader is referred to the Preface for brief background information on the current relationship between the United States and Iran.

with a goal of improving disease prevention and limiting the progression of diseases

- Applying best microbiological methods and practices—including purchasing appropriate equipment
- Using database networks such as FoodNet and PulseNet to identify foodborne diseases related to food production in Iran

In addition, looking forward to future joint workshops in Iran, several suggestions were made about strengthening the exchange of information at such workshops. The suggestions included the following:

- *Incorporating into the formal workshop experiences from field visits and the conclusions of interdisciplinary discussions with experts in related fields.* This could involve including reports on site visits in the United States, followed by planning for future collaboration between the United States and Iran.

- *Integrating additional scientific disciplines, including basic sciences in fields such as chemistry.* As noted by several Iranians, the basic sciences have in many ways been segregated from medical science in recent years. Thus, work may be needed to convince Iranian leaders to adequately integrate these fields once again.

- *Developing programs and strategies to bring together the natural sciences and the medical sciences.* This would be consistent with efforts being made in both countries to integrate medical research training on a broad basis.

## OTHER FORMS OF COLLABORATION

Participants expressed interest in the exchange of ideas, information, and experience among Iranian and U.S. colleagues on a variety of topics. These topics include the following:

- Conducting well-designed studies to obtain the type of data that will inform strategies for the prevention of foodborne illness
- Establishing an effective foodborne disease surveillance system and outbreak investigation program
- Reporting on relevant clinical trials

Several strategies were suggested for facilitating collaboration between the countries. These included the following:

- *Arranging for student exchanges and faculty visits.* The National Academies or the U.S. Department of State may be able to help facilitate faculty visits, but neither is involved in student exchanges.

- *Collaboration between international laboratorians and state public health laboratorians.* This might be facilitated by the Association of Public Health Laboratories.

- *Assisting Iranian researchers to identify and make contact with potential U.S. colleagues in universities.* U.S. participants in this workshop might be able to facilitate introductions—especially while the Iranians are on their U.S. tour. For the names of U.S. scientists who might be able to collaborate with Iranian scientists in the study of specific microorganisms, Doyle suggested that the Iranian scientists submit a list of the pathogens of interest and the names of appropriate Iranian contacts.

- *Training programs.* Schweitzer indicated that licenses may be required for programs involving training. Training in quality assurance and quality-control procedures for international laboratorians is offered by the Association of Public Health Laboratories in cooperation with George Washington University.

- *Publications having Iranian authors.* Schweitzer reported that several years earlier a general license was issued by the U.S. government to permit publication of Iranian reports in the United States even if they required considerable revision and editing by American publishers; the license also facilitates the preparation of joint U.S.–Iranian publications.

- *Membership in professional societies.* Schweitzer reported that services offered by professional societies may also be subject to licenses and noted that this issue compelled the American Chemical Society to cancel Iranian membership. This problem has been partially resolved, however, and members have been reinstated.

- *Institutional relationships.* The Bureau of Educational and Cultural Exchanges of the U.S. Department of State encourages the establishment of institutional relationships. The U.S. Department of State provided financial support for this workshop.

Larry A. Moody, speaking on behalf of the U.S. Department of State, indicated that he knew of no restrictions on U.S. citizens traveling to Iran in furtherance of collaborative efforts in non-sensitive areas other than the need to receive a visa from Iran. Participants were cautioned, however, that the transfers of money or equipment could cause problems. Ardalan noted that it had been possible to transfer money through the Iranian Epidemiological Association as part of an official epidemiology project with the University of California at Los Angeles.

Yazdanparast suggested expanding collaborative efforts to more Iranian universities.

With regard to collaborative relationships, Keene noted that they are easier to establish in fields that are universal in methodology and intellectual approach than in areas such as clinical trials and disease surveillance.



Essentially all the public health surveillance activities in the United States are managed by state and local governments. This local responsibility in the United States may limit the possibility of establishing official relationships between experts in the two countries.

Moreover, Keene noted that surveillance activities and outbreak investigations involve many practical problems—problems that may be peculiar to the particular state or country in question. One such problem in the United States relates to the various options that telephone customers have to limit their accessibility via phone. A growing number of telephone customers, for example, are choosing to have unlisted telephone numbers, and many of them also use call-screening methods to decide which calls they will answer. Such options make it more difficult to reach patients in order to collect necessary information for studies. Because legal authority and various practical matters differ from one country to the other, surveillance systems that work well in many American states may need to be adapted considerably if they are to fit with approaches of Iranian institutions and social customs.

Iranian participants indicated that among the steps they might be able to take to strengthen field laboratories would be a series of training workshops and the outfitting of facilities so that they will meet the minimum requirements of surveillance systems.

### CLOSING REMARKS

On behalf of the Iranian scientists, Mohammad Reza Zali expressed sincere appreciation for the opportunity to meet with U.S. colleagues. Recognizing that both countries have many problems, he said that he views the establishment and expansion of scientific relationships to be an important step for scientists and also for the general populations in both countries. Doyle expressed appreciation to all those involved in carrying out an excellent workshop. He said that the presentations had been of high quality and commended the Iranians for the excellent research they are conducting. Both moderators expressed the hope that collaborations between scientists in the two countries may flourish, resulting in improved science and improved health.

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# Appendix A

## Workshop Agenda

**Food Safety and Microbiology: An Exchange of Ideas and Experiences**  
The National Academies 2100 C Street, NW, Washington, DC  
November 13–15, 2007

**Objective: A forum for Iranian and American experts to exchange ideas on:**

- **Food Safety and Microbiology**
- **Potential Association of Foodborne and Chronic Diseases**
- **Further Collaboration to Advance in Areas of Interest**

### **November 13—Lecture Room**

**9:00 a.m. Welcome**

*Glenn Schweitzer, Director, Office of Eastern Europe and Eurasia, National Research Council*

*Linda D. Meyers, Director, Food and Nutrition Board, Institute of Medicine*

*Mohammad Reza Zali, Shaheed Beheshti University of Medical Sciences*

*Michael Doyle, Co-Chair, Food and Nutrition Board, Institute of Medicine*

**SESSION 1: FOOD SAFETY AND MICROBIOLOGY**

*Moderator: Mohammad Mehdi Aslani, Department of Microbiology,  
Institute Pasteur of Iran*

**9:30 a.m. Progress on the Iranian Foodborne Disease Surveillance Pilot Project**

*Ali Ardalan, Tehran University of Medical Sciences,  
Tehran, Iran*

*Mohammad Mehdi Aslani, Institute Pasteur of Iran*

*Fereshteh Jafari, Shaheed Beheshti University of Medical  
Sciences*

*Hosein Dabiri Jaldebakhani, Shaheed Beheshti University  
of Medical Sciences*

*Nahid Arjmand Kermani, Shaheed Beheshti University of  
Medical Sciences*

*Ehsan Nazemalhoseini Mojaradn, Shaheed Beheshti  
University of Medical Sciences*

*Maryam Sanaei, Shaheed Beheshti University of Medical  
Sciences*

**10:20 a.m. BREAK**

**10:45 a.m. Foodborne Disease Surveillance in the United States**

*Robert V. Tauxe, Centers for Disease Control and Prevention*

**11:15 a.m. PulseNet**

*Jennifer A. Kincaid, Centers for Disease Control and  
Prevention*

**11:30 a.m. Discussion**

**12:30 p.m. LUNCH (Members Room)**

**2:00 p.m. Current Technical and Scientific Aspects of Foodborne Diseases in Iran**

*Mohamad Mehdi Aslani, Department of Microbiology,  
Institute Pasteur of Iran*

**3:00 p.m. Burden of Gastrointestinal Disease in Iran**

*Mohammad Reza Zali, Shaheed Beheshti University of  
Medical Sciences*

**3:30 p.m. Discussion**

**4:30 p.m. Adjourn**

**November 14—Lecture Room****SESSION 2: RISK ASSESSMENT: METHODOLOGIES  
APPLICATION TO FOOD MICROBIOLOGY**

*Moderator: Karl R. Matthews, Rutgers University*

**9:00 a.m. Risk Assessment Methodologies**  
*Robert Buchanan, Food and Drug Administration*

**9:30 a.m. Evaluation of Risk–Risk Trade-Offs**  
*Richard A. Forshee, University of Maryland*

**10:00 a.m. Discussion**

**11:00 a.m. Break**

**SESSION 3: POTENTIAL ASSOCIATION OF FOODBORNE AND  
CHRONIC DISEASES**

*Moderator: J. Glenn Morris, Jr., University of Florida*

**11:30 a.m. Signaling Pathways in Cancer**  
*Ali Ardalan, Tehran University of Medical Sciences*  
*Ali Ghanbari Motlagh, Cancer Center, Shaheed Beheshti*  
*Medical University*  
*Razieh Yazdanparast, Institute of Biochemistry and Biophysics,*  
*University of Tehran*  
*Narges Zali, Cancer Center, Shaheed Beheshti Medical*  
*University*

**12:30 p.m. LUNCH (Members Room)**

**2:00 p.m. Characterization of Intestinal Flora and Its Relationship  
to Cancer**  
*Volker Mai, University of Florida*

**2:30 p.m. Human Microbiome Project**  
*Lu Wang, National Human Genome Research Institute,*  
*National Institutes of Health*

**2:45 p.m. Discussion**

**3:45 p.m. Break**

**SESSION 4: APPROACHES TO HEALTH EDUCATION**

*Moderator: Ali Ardalan, Tehran University of Medical Sciences*

**4:00 p.m.      A Vision for Integrated Medical Research Training at UCSF**

*Keith Yamamoto, University of California, San Francisco*

**4:30 p.m.      Health Education Approach in Iran**

*Mohammad Reza Zali, Shaheed Beheshti University of Medical Sciences*

**5:00 p.m.      Discussion**

**5:30 p.m.      Adjourn**

**November 15—Lecture Room**

**SESSION 4: HIGHLIGHTS OF U.S. VISIT AND FURTHER  
COLLABORATION TO ADVANCE IN AREAS OF INTEREST**

*Moderators: Michael Doyle and Mohammad Reza Zali*

**9:00 a.m.      Future Needs for an Effective Surveillance System**

**10:00 a.m.      Future Opportunities for Collaboration**

**11:00 a.m.      Closing Remarks**

**11:30 a.m.      Adjourn**



# Appendix B

## Workshop Participants

**Sana Abed-Kotob**

U.S. Department of State  
Washington, DC  
sana.abed-kotobs@state.gov

**Dr. Ali Ardalan**

Assistant Professor  
Health in Emergency & Disaster  
Division  
Institute of Public Health Research  
School of Public Health & IPHR  
Tehran University of Medical  
Sciences  
Tehran, Iran  
Phone: 0098-21-88951401  
Fax: 0098-21-88951401  
aardalan@gmail.com

**Dr. Mohammad Mehdi Aslani**

Head, Enterobacteriaceae  
Laboratory  
Institute Pasteur of Iran  
No. 69, Pasteur Avenue, 13169  
Tehran, Iran  
Phone: 009-82166405535  
Fax: 009-82166465132  
mmaslani@yahoo.com, mmaslani@  
pasteur.ac.ir

**Ms. Beverly H. Attallah**

Vice President and Director  
Center for International Exchanges  
Academy for Educational  
Development  
1825 Connecticut Avenue, NW  
Washington, DC 20009  
Phone: 202-884-8223  
Toll-Free: 800-634-8956  
battalla@aed.org

**Dr. Habib Bagheri**

Associate Professor, Analytical  
Chemistry  
Department of Chemistry  
Sharif University of Technology  
Azadi Avenue 11365-9516  
Tehran, Iran  
Phone: 0098-21-6005718  
Fax: 0098-21-6012983  
bagheri@sharif.edu

**John Besser**

Clinical Laboratory Manager  
Public Health Laboratory  
Minnesota Department of Health  
601 Robert Street North  
St. Paul, MN 55164-0899  
Phone: 651-201-5066  
Fax: 651-201-5070  
john.besser@health.state.mn.us

**Dr. Larry R. Beuchat**

Distinguished Research Professor  
Center for Food Safety  
Department of Food Science &  
Technology  
University of Georgia  
1109 Experiment Street  
Griffin, GA 30223-1797  
Phone: 770-412-4740  
Fax: 770-229-3216  
lbeuchat@uga.edu

**Dr. Arvind A. Bhagwat**

Lead Scientist and Research  
Microbiologist  
Produce Quality & Safety  
Laboratory  
Agriculture Research Services  
U.S. Department of Agriculture  
10300 Baltimore Avenue  
Bldg. 002 Barc-West  
Beltsville, MD 20705-2350  
Phone: 301-504-5106  
Fax: 301-504-5107  
arvind.bhagwat@ars.usda.gov

**Dr. Robert L. Buchanan**

Senior Science Advisor  
Center for Food Science and  
Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835  
Phone: 301-436-2642  
robert.buchanan@fda.hhs.gov

**Dr. Cindy D. Davis**

Program Director  
Nutritional Science Research  
Group  
Division of Cancer Prevention  
National Cancer Institute  
6130 Executive Blvd. MSC 7315  
Bethesda, MD 20892-7315  
davisci@mail.nih.gov

**Dr. Michael P. Doyle**

Regents Professor of Food  
Microbiology  
Director, Center for Food Safety  
University of Georgia  
1109 Experiment Street  
Griffin, GA 30223  
Phone: 770-228-7284  
Fax: 770-229-3216  
mdoyle@uga.edu

**Dr. Mohammad Ali Esmaeili**

Professor and Researcher  
Institute of Biochemistry and  
Biophysics  
University of Tehran  
No. 174 Nastaran Alley  
Tehran, Iran  
Phone: 0098-21-66113382  
Fax: 0098-21-66404680  
esmaeli@ibb.ut.ac.ir

**Dr. Richard A. Forshee**

Deputy Director & Director of  
Research  
Center for Food, Nutrition &  
Agriculture Policy  
1122 Patapsco Building  
College Park, MD 20742-6726  
Phone: 301-405-8222  
Fax: 301-405-7979  
rforshee@umd.edu

**Dr. Eugene Gangarose**

Gangarose International Health  
Foundation  
5305 Greencastle Way  
Stone Mountain, GA 30087-1427  
Phone: 770-491-0688  
Ejg1926@aol.com

**Dr. Heather Green**

Food Safety Program Manager  
Association of Public Health  
Laboratories  
8515 Georgia Avenue, Suite 700  
Silver Spring, MD 20910  
Phone: 240-485-2759  
Fax: 240-485-2700  
heather.green@aphl.org

**Dr. George J. Jackson**

Microbiologist (Retired)  
U.S. Food and Drug  
Administration  
Washington, DC  
gorgon7@his.com

**Ms. Fereshteh Jafari**

Researcher  
Research Center for  
Gastroenterology and Liver  
Diseases  
Tehran University of Medical  
Sciences  
Shaheed Beheshti University of  
Medical Sciences  
7th Floor, Taleghani Hospital  
Yaman Avenue, Tabnak Street  
Velenjak  
Tehran, Iran  
Phone: 0098-21-22432514-18  
Fax: 0098-21-22432518  
Tehran, Iran  
F\_jaafari580@yahoo.com

**Dr. Hosein Dabiri Jaldebakhani**

Researcher  
Research Center for  
Gastroenterology and Liver  
Diseases  
Shaheed Beheshti University of  
Medical Sciences  
Tehran University of Medical  
Sciences  
7th Floor, Taleghani Hospital  
Yaman Avenue, Tabnak Street  
Velenjak  
Tehran, Iran  
Phone: 0098-21-22432514-18  
Fax: 0098-21-22432518  
hdabiri@razi.tums.ac.ir

**Dr. Sam W. Joseph**

Emeritus Professor  
Department of Cell Biology and  
Molecular Genetics  
1109 Microbiology Building  
College Park, MD 20742  
Phone: 301-405-5452  
Fax: 301-314-9489  
swj@umd.edu

**Dr. William E. Keene**

Senior Epidemiologist  
Acute and Communicable Disease  
Division  
Oregon Department of Human  
Services  
800 NE Oregon, Suite 772  
Portland, OR 97232  
Phone: 503-731-4024  
Fax: 503-731-4798  
keene@cluemail.com

**Dr. Nahid Arjmand Kermani**

Research Assistant  
Research Center for  
Gastroenterology and Liver  
Diseases  
Shaheed Beheshti University of  
Medical Sciences  
7th Floor, Taleghani Hospital  
Yemen Street, Evin  
Tehran, Iran  
Phone: 0098-21-66516276  
nahid\_arjmand\_k@yahoo.com

**Dr. Ali Khalaj**

Professor of Medicinal Chemistry  
Faculty of Pharmacy  
Tehran University of Medicinal  
Sciences  
Enghelab Avenue  
Tehran, Iran  
Phone: 0098-21-88962007  
Fax: 0098-21-66461178  
khalaj@ams.ac.ir

**Ms. Jennifer A. Kincaid**

PulseNet National Database Team  
Centers for Disease Control and  
Prevention  
8515 Georgia Avenue, Suite 700  
Silver Spring, MD 20910  
Phone: 240-485-2795  
Fax: 240-485-2700  
JKincaid@cdc.gov

**Dr. Yaguang Luo**

Research Food Technologist  
Produce Quality and Safety Lab  
Agricultural Research Service  
U.S. Department of Agriculture  
10300 Baltimore Avenue  
Bldg. 002 Barc-West  
Beltsville, MD 20705-2350  
Phone: 301-504-6186  
Fax: 301-504-5107  
yaguang.luo@ars.usda.gov

**Dr. Volker Mai**

Assistant Professor  
Microbiology and Cell Science  
Emerging Pathogen Institute  
University of Florida  
Bldg. 981, Room 1247  
P.O. Box 110700  
Gainesville, FL 32611-0700  
Phone: 352-846-0956  
Fax: 352-392-5922  
vmai@ufl.edu

**Dr. Karl R. Matthews**

Associate Professor  
Department of Food Science, Cook  
College  
Rutgers, The State University of  
New Jersey  
65 Dudley Road  
New Brunswick, NJ 08901-8520  
Phone: 732-032-9611, ext. 219  
Fax: 732-932-6776  
matthews@aesop.rutgers.edu

**Dr. Crystal McDade-Ngutter**

Health Program Specialist  
National Institutes of Health  
Division of Nutrition  
Research Coordination  
6707 Democracy Blvd  
Bethesda, MD 20817  
Phone: 301-451-2064  
cm585d@nih.gov

**Dr. Linda D. Meyers**

Director  
Food and Nutrition Board  
Institute of Medicine  
500 Fifth Street, NW  
Washington, DC 20001  
Phone: 202-334-1732  
Fax: 202-334-1917  
lmeyers@nas.edu

**Dr. Manijeh Mianabadi**

Researcher  
Gorgan University of Medical  
Sciences  
P.O. Box 49138-15739  
Gorgan, Iran  
Phone: 0098-17-14427040  
Fax: 0098-17-14427040  
mianabadi@ibb.ut.ac.ir

**Dr. Sanford A. Miller**

Senior Fellow  
Center for Food, Nutrition, and  
Agriculture Policy  
Affiliated Professor Nutrition and  
Food Science  
University of Maryland, College  
Park  
Room 1122, Patapsco Building  
College Park, MD 20742-6726  
Phone: 301-405-9470  
Fax: 301-405-7979  
millersa@umd.edu

**Dr. Seyedreza Mohebbi**

Ph.D. Student and Researcher in  
Medical Virology  
Research Center for  
Gastroenterology and Liver  
Diseases  
7th Floor, Taleghani Hospital  
Yaman Avenue, Tabnak Street  
Velenjak  
Tehran, Iran  
Phone: 0098-21-22432525  
Fax: 0098-21-22432517  
srmohebbi@rcgld.org

**Mr. Ehsan Nazemalhoseini  
Mojarad**

Medical Parasitologist  
Department of Foodborne and  
Diarrhea Disease  
Shaheed Beheshti University of  
Medical Sciences  
7th Floor, Taleghani Hospital  
Temen Street, Evin  
Tehran, Iran  
Phone: 0098-21-22432518  
Fax: 0098-21-22432518  
ehsan\_nazem\_m@yahoo.com

**Mr. Larry A. Moody**

Program Officer  
U.S. Department of State  
North Africa, Near East, South  
and Central  
301 4th Street, SW  
Washington, DC  
Phone: 202-453-8612  
moodyla@state.gov

**Dr. J. Glenn Morris, Jr.**

Director  
Emerging Pathogens Institute  
University of Florida  
S. Newell Drive, Bldg 62  
P.O. Box 100009  
Gainesville, FL 32610  
Phone: 352-273-7526  
Fax: 352-273-6890  
jgmorris@ufl.edu

**Dr. Ali Ghanbari Motlagh**

Head, Jorjiani Cancer Branch  
Research Center for  
Gastroenterology and Liver  
Diseases  
Shaheed Beheshti Medical  
University  
Jorjiani Cancer Center, Imam  
Hossein Hospital  
Shahid Madani Avenue  
Tehran, Iran  
Phone: 0098-21-22427432  
agmotlagh@yahoo.com

**Dr. Nosratollah Naderi**

Assistant Professor and Research  
Director  
Department of Inflammatory  
Bowel Disease  
Research Center for  
Gastroenterology and Liver  
Diseases  
Shaheed Beheshti University of  
Medical Sciences  
7th Floor, Taleghani Hospital,  
Velenjak 19857  
Tehran, Iran  
Phone: 0098-21-22432525  
Fax: 0098-21-22432517  
n\_naderi@yahoo.com

**Dr. Maria Oria**

Senior Program Officer  
Food and Nutrition Board  
Institute of Medicine  
500 Fifth Street, NW  
Washington, DC 20001  
Phone: 202-334-2321  
Fax: 202-334-2316  
moria@nas.edu

**Dr. Mansour Samadpour**

Institute for Environmental  
Health, Inc.  
15300 Bothell Way NE  
Lake Forest Park, WA 98155  
Phone: 206-660-5090  
Fax: 206-306-8883  
ms@iehinc.com

**Ms. Maryam Sanaei**

Department of Foodborne and  
Diarrhea Disease  
Research Center for  
Gastroenterology and Liver  
Diseases  
Shaheed Beheshti University of  
Medical Sciences  
Tehran, Iran  
sanaeimaryam@yahoo.com

**Mr. Glenn Schweitzer**

Director, Office for Central Europe  
and Eurasia  
National Academies  
500 Fifth Street, NW  
Washington, DC 20001  
Phone: 202-334-2172  
gschweitzer@nas.edu

**Ms. Leila Shokrzadeh**

Researcher  
Department of Foodborne and  
Diarrhea Disease  
Research Center for  
Gastroenterology and Liver  
Diseases  
7th Floor, Taleghani Hospital  
Yaman Street, Evin  
Tehran, Iran  
Phone: 0098-21-66843846  
Fax: 0098-21-22432518  
Leila\_shokrzadeh@yahoo.com

**Dr. Carol West Suitor**

Nutrition Consultant  
Northfield, VT

**Dr. Robert Tauxe**

Acting Deputy Director  
Division of Foodborne, Bacterial  
and Mycotic Diseases  
National Center for Zoonotic,  
Vectorborne, and Enteric  
Diseases (Mailstop C-09)  
Centers for Disease Control and  
Prevention  
Atlanta, GA 30333  
rvt1@cdc.gov

**Dr. Lu Wang**

Program Director  
Large Scale Sequencing  
National Human Genome  
Research Institute  
National Institutes of Health  
5635 Fishers Lane, Suite 4105 MSC  
9305  
Bethesda, MD 20892  
Phone: 301-594-7303  
Fax: 301-480-2770  
wanglu@mail.nih.gov

**Dr. Keith Yamamoto**

Professor  
Cellular and Molecular  
Pharmacology Dept.  
Executive Vice Dean  
University of California, San  
Francisco  
School of Medicine  
600 16th Street, Genentech Hall,  
GH-S574  
San Francisco, CA 94143-2280  
Phone: 415-476-3128  
Fax: 415-476-6129  
yamamoto@cmp.ucsf.edu

**Dr. Razieh Yazdanparast**

Professor in Medicinal Chemistry  
and Pharmacognosy  
Institute of Biochemistry and  
Biophysics  
University of Tehran  
Tehran, Iran  
Phone: 98-21-66956976  
yazdan@ibb.ut.ac.ir

**Dr. Mohammad Reza Zali**

Professor of Medicine  
Shaheed Beheshti University  
Director, Research Center for  
Gastroenterology and Liver  
Diseases  
7th Floor, Taleghani Hospital  
Yaman Street, Evin  
Tehran, Iran  
Phone: 0098-21-2417283  
Fax: 0098-21-2402639  
mzali@hotmail.com

**Ms. Narges Zali**

Student, Molecular Medicine  
Shaheed Beheshti University of  
Medical Sciences  
7th Floor, Taleghani Hospital,  
Parvaneh Avenue  
Tabnak Street, Evin  
P.O. Box 19835-187  
Tehran, Iran  
Phone: 0098-21-22432521  
Fax: 0098-21-22432515  
nzali@rcgld.org



# Appendix C

## Site Visits

### **Washington, DC, area, November 16 and November 30, 2007**

Food and Drug Administration  
5100 Paint Branch Parkway  
(HFS-1)  
College Park, MD 20740-3835

National Cancer Institute  
National Institutes of Health  
6130 Executive Boulevard  
Rockville, MD 20892

### **Portland, Oregon, November 17–November 21, 2007**

Department of Health and Human  
Services  
Oregon Public Health Division  
800 NE Oregon Street  
Portland, OR 97232

Oregon Health & Science  
University

3181 S.W. Sam Jackson Park Road  
Portland, OR 97239-3098

Multnomah County Health  
Department

3181 S.W. Sam Jackson Park Road  
Portland, Oregon 97239-3098

### **Seattle, Washington, November 21–November 24, 2007**

IEH Laboratories & Consulting  
Group

15300 Bothell Way NE  
Lake Forest Park, WA 98155

**Griffin, Georgia, November  
24–November 28, 2007**

University of Georgia  
Center for Food Safety  
1109 Experiment Street  
Griffin, GA 30223

Food Safety Task Force  
Georgia Department of  
Agriculture  
19 Martin Luther King, Jr. Dr., SW  
Atlanta, Georgia 30334

Georgia Division of Public Health  
Office of Public Health Practice  
2 Peachtree Street, NW, 15-295  
Atlanta, GA 30303

Emory University  
Emory Children's Center  
Division of Gastroenterology  
2015 Uppergate Drive, NE  
Atlanta, GA 30322

# Appendix D

## Abbreviations

BRAF	B-type Raf kinase
CDC	U.S. Centers for Disease Control and Prevention
DNA	deoxyribonucleic acid
ERK	extracellular signal-regulated kinase
FAP	familial adenomatous polyposis
FDA	U.S. Food and Drug Administration
FNB	Food and Nutrition Board
GERD	gastrointestinal esophageal reflux disease
3-HK	3-hydrogenkwadaphnin
HNPCC	hereditary nonpolyposis colorectal cancer
IHC	immunohistochemistry
IOM	Institute of Medicine
IQ	intelligence quotient
JNK	Jun N-terminal kinase
MMR	mismatch repair
MSI	microsatellite instability
NIH	National Institutes of Health

PCR	polymerase chain reaction
PGFE	pulsed-field gel electrophoresis
QALY	quality-adjusted life year
RCGLD	Research Center for Gastroenterology and Liver Diseases
RDFD	Research Department of Foodborne and Diarrheal Diseases
STEC	Shiga toxin-producing <i>E. coli</i>
U.S.	United States
USA	United States of America
USDA	U.S. Department of Agriculture
WHO	World Health Organization