CHAPTER 1

INFRASTRUCTURE OVERVIEW

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INTRODUCTION TO THE STUDY

Biosensing technologies comprise portable devices and systems used for identifying, monitoring, and controlling biological phenomena. Most of these technologies have come into use just in the last two decades; nevertheless, biosensing already garners major academic, government, and industry R&D funding; relies on highly sophisticated multidisciplinary technology; and enjoys well developed and growing markets. Prior to September 11, 2001, U.S. biosensing development was driven primarily by the requirements of medical diagnostics, environmental monitoring, and food safety assurance. Since September 11, worries about anthrax, smallpox, and or other biological "weapons" in the hands of terrorists have elevated the prominence of biosensing as a component of bio-warfare defense. Adding to the rapidly growing significance of biosensing is its place in the remarkable convergence of advanced bio-, nano-, and infotechnologies in a totally new scientific paradigm.

With these trends as background, in May 2002, five U.S. government agencies asked the World Technology Evaluation Center (WTEC) to investigate states of the art and trends in biosensing research and development worldwide in comparison to the United States. The National Science Foundation (NSF), National Institutes of Health (NIH), United States Department of Agriculture (USDA), National Aeronautics and Space Administration (NASA) and Army Research Office (ARO) intend for this biosensing study to

- aid government policymakers, the research community, and the public to identify good ideas worth exploring in U.S. R&D programs
- note technical, educational, and infrastructure requirements and prospects for better progress in the field

- ascertain opportunities for international and interdisciplinary collaboration
- identify ways to shorten the lead time for deploying new biosensing technologies emerging from the lab
- evaluate the status and funding of foreign research programs relative to those in the United States

The study's sponsors identified particular applications of interest to be *healthcare* (biomedicine), the *environment*, the *food industry*, and *defense* against the threats of chemical and biological agents. The sponsors further identified the following specific technical issues to be addressed:

- nucleic acid sensors and DNA chips and arrays
- organism- and cell-based biosensors
- bioelectronics and biometrics
- biointerfaces and biomaterials, biocompatibility, and biofouling
- integrated, multimodality sensors and sensor networks
- system issues, including signal transduction, data interpretation, and validation
- novel sensing algorithms, e.g., non-enzyme-based sensors for glucose, or mechanical sensors for prosthetics
- related issues in bio-MEMS and bio-NEMS (microelectromechanical and nanoelectromechanical systems), possibly including actuators

Approach and Methodology

To execute the biosensing study, WTEC recruited a panel of seven U.S. experts in the field, chaired by Professor Jerome Schultz, then of the University of Pittsburgh, now at University of California, Riverside. The panelists each represent distinct areas of specialization in the biosensing field. Table 1.1 lists the panelists and their areas of focus for the study, along with others who helped arrange, conduct, and evaluate the site visits. Panelists' biographies are provided in Appendix A.

With the goals and team established, the WTEC panelists carried out the study in four phases:

1. *Establish baseline information on U.S. activities* as a benchmark for the worldwide assessment by hosting a workshop of members of the U.S. biosensing R&D community. The WTEC Biosensing Study U.S. R&D Overview Workshop was held at NIH in Bethesda, MD, on 3–4 December 2002. Participants provided an overview of recent trends and advances in biosensing technology development in the

areas identified by the sponsors; addressed the barriers for translating these technologies into the marketplace; and identified several general needs and applications that should be addressed in future R&D plans and programs. Proceedings of the workshop are available online at wtec.org / biosensing / proceedings /.

2. *Conduct site visits to gather first-hand information* from a number of the world's best university and industrial laboratories in biosensing research. The WTEC panelists conducted two week-long series of site visits to 23 laboratories in Europe and Australia and 17 laboratories in Japan during January and March 2003, respectively. Site reports of those visits are included in this report as Appendixes B and C and are also listed by name in the Table of Contents of this report.

Table 1.1.
Key Members of the WTEC Team and Their Roles in the Biosensing Study

Name	Organization	Assignment	Technical Focus
Jerome Schultz	University of Pittsburgh	Panel chair	Infrastructure
Milan Mrksich	The University of Chicago	Panel vice chair	Electrochemical/surface treatment
David Walt	Tufts University	Panel member	Optical sensing
Sangeeta Bhatia	University of California, San Diego	Panel member	Biological/cellular sensing
Charles Wilkins	University of Arkansas	Panel member	Mass spectrometry
Antonio Ricco	ACLARA BioSciences	Panel member	Microfluidics
David Brady	Duke University	Panel member	Data fusion/system integration
Fred Heineken	NSF/Engineering	Sponsor/Observer	
Christine Kelley	NIH, Institute for Biomedical Imaging and Bioengineering (NIBIB)	Sponsor/Observer	
Hassan Ali	WTEC	Support staff	

3. *Report back findings in a public forum* to the U.S. sponsors, the biosensing scientific community, and the public at large. The WTEC Workshop on Biosensing in Europe, Japan, and the United States was held on 13 May 2003 at the Bethesda, MD, Marriott Hotel. This workshop served as an open forum for presentation, discussion, and critical review of the panel's findings among members of the panel and invited participants. Viewgraphs from this workshop are available online at wtec.org/biosensing/views/.
4. *Compile the results of the study findings* from the first three phases into a written report to be made available to the funding agencies, to policymakers, and to the public. Each panel member prepared a chapter describing and analyzing what has been found in a specific area of biosensing in Japan and Europe and compared that with the status of that R&D in the United States. Before publication of this report, sponsoring agencies and site visit hosts reviewed drafts of the chapters and site reports and made corrections of factual statements, as applicable. As well as being available in print, this report is available on the Web at www.wtec.org/biosensing.

The term "biosensing" has been used throughout the WTEC study and in this report to mean not just devices but *systems* that produce verifiable signals for detecting biological occurrences through a variety of means, for a variety of purposes. Biosensing systems can include electrical, electronic, photonic, or mechanical devices; biological materials such as tissue, enzymes, or nuceic acids; means to provide chemical analysis; and advanced imaging and information processing technologies. Biosensors, which are devices that employ biological mechanisms or materials to provide selectivity and amplification for sensing biochemical materials, often are components of biosensing systems.

Report Structure

This final report is organized by chapter along the lines of the discrete foci of the individual panelists, based on information obtained through their individual expertise, offline research (a literature review), Europe and Japan site visits, and the May 2003 U.S. workshop presentations. The core of this first chapter outlines the cross-cutting issues related to infrastructure, comparing the status and strategies for investment in research as well as in physical and human resources in the United States, Europe, and Japan. Chapter 2 by David Walt discusses activities in optical biosensing, highlighting the scientific findings and outlining the challenges ahead. In Chapter 3, Milan Mrksich provides an overview and regional comparison of the development and implementation of electro-based sensors and surface engineering. Sangeeta Bhatia discusses in Chapter 4 the power of cell-based sensors to push the frontiers of biosensing by leveraging the unique attributes of living systems; her chapter provides an overview and regional comparisons of the latest developments in cell- and tissue-based sensors for both clinical and non-clinical applications. Chapter 5 by Charles Wilkins reviews the major work and research centers on mass spectrometry and biosensing research in the three regions and reveals the emerging trends. Chapter 6 by Antonio Ricco reviews the R&D activities in biosensing that are based on microelectromechanical systems, or MEMS, including their relationship to the field now broadly known as nanotechnology. Finally, David Brady in Chapter 7 addresses how biosensing research integrates biochemistry, physical electronics, and information systems, highlighting how each of the three regions pursues research in biosensing information systems and pointing out the opportunities in system integration.

HISTORY OF BIOSENSING DEVELOPMENT

To put the current high level of interest and research activity into perspective and to set the context for the chapters that follow, it is useful to briefly review the history of chemical sensors and biosensors. The use of the term "sensor" usually refers to a device that is somewhat portable in nature and that can be placed into an environment of interest, often a liquid sample, to measure a specific chemical (an analyte) on-site. This is in contrast to the traditional procedure of sending samples to a chemical or clinical analytical laboratory, where a variety of instruments are employed. The earliest chemical sensor of this type is the glass pH electrode that was developed in 1922 and later implemented as a portable device. It took almost another third of a century before the next practical chemical sensor was developed, the oxygen electrode invented by Leland Clark in 1954. Dr. Clark later introduced the concept of a biosensor in 1962 through his invention of the glucose electrode. Since then, the introduction and development of many different kinds of sensor technologies have been increasingly rapid. Table 1.2 lists some of development highlights.

A brief description of the Clark glucose electrode is instructive, because the components of this sensor device recur in most biosensors that have been developed subsequently. Figure 1.1 shows the components of this device, as published by Dr. Clark in 1962. In brief, the operation of this sensor is based on the reduction of oxygen flux to the oxygen electrode due to the consumption of oxygen in the *biosensing layer* (labeled F in the figure, comprised of enzymes glucose oxidase and peroxidase), by the oxidation of glucose to gluconic acid. The greater the concentration of glucose in the external media (and also in layer F), the lower the flux of oxygen to the electrode.

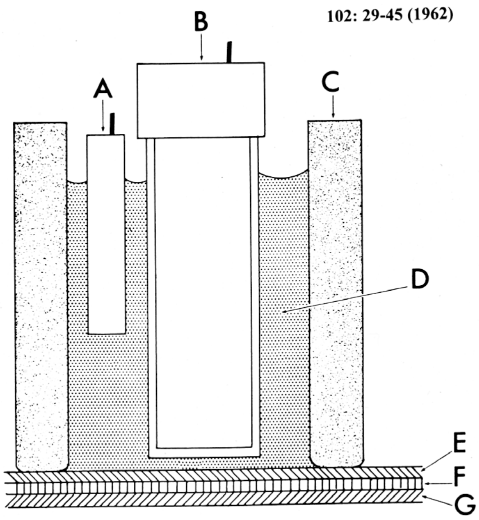

Fig. 1.1. First "enzyme" electrode—an electrode system for continuous monitoring in cardiovascular surgery. In this diagram, the elements marked A through E comprise the amperometric oxygen electrode. Addition of layer "F" containing the enzymes glucose oxidase and peroxidase converted this chemical sensor into a biosensor. Layer "G" is a semipermeable membrane that allows both glucose and oxygen to pass into the sensor. (Clark and Lyons 1962)

Table 1.2.
History of Chemical and Biological Sensors

Sensor Technology	**Inventor**	**Date**
Glass pH Electrode	Hughes	1922
Oxygen Electrode	Clark	1954
Carbon Dioxide Electrode	Stow and Randall	1954
Glucose Electrode	Clark	1962
Potentiometric Sensor	Guilbault	1969
Immunosensor	Janata	1975
Optodes	Lubbers	1975
Optical Affinity Sensors	Schultz	1979
Chip-Based Technologies	Fodor	1991

The essential components of a biosensor are a *detection capability* in this case, the oxygen electrode) and a *biological recognition capability* in this case, the enzyme layer). After Dr. Clark's invention, the research community realized that many detector systems can be used, and that many recognition materials can be found in nature. Figure 1.2 shows a simplified matrix that can lead to a variety of combinations of molecular recognition elements and transducers to produce biosensors, such as an antibody placed at the end of a fiberoptic system or a membrane receptor immobilized on a piezoelectric crystal. In the last few decades, the pace of biosensor research has increased dramatically, as described in thousands of journal articles, hundreds of patents, and dozens of books (several references are listed at the end of this chapter).

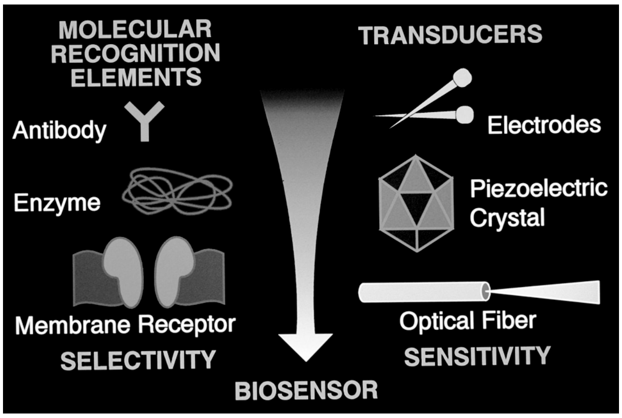

Fig. 1.2. A simplified matrix that can lead to a variety of combinations of molecular recognition elements and transducers to produce biosensors.

TECHNOLOGY DRIVERS

A number of factors have been driving interest and investment in biosensor research and product development. The primary driver has been the public's demand for healthcare aides, in particular ones to assist diabetics to cope with their disease. NIH conducted a major study during the period 1983–1993, called the Diabetes Control and Complications Trial, where approximately 1,500 individuals with Type 1 diabetes maintained close control of their blood sugar levels by self-testing about five times per day and administering insulin as needed to bring their blood sugar levels within the normal range. Those individuals who were able to maintain this regime of testing and control exhibited a remarkable reduction in the complications normally found in diabetics: risk of eye disease was reduced 76%, risk of kidney disease was reduced 50%, and risk of nerve disease was reduced 60%. Because of this fantastic outcome, development of more convenient blood glucose testing methods has become a major goal of the research and commercial communities. The current worldwide market for blood glucose testing equipment and test strips is estimated to be on the order of a billion dollars per year, and hundreds of millions of dollars have been spent on new sensing technologies for this purpose (see articles in the journal *Diabetes Technology and Therapeutics*).

This extended interest and investment in methods for blood glucose sensing has led to many new technologies, and researchers have been able to tap into this wealth of knowledge to apply sensing technologies for measuring biochemicals to other types of disease prevention and "wellness" maintenance. An example of this trend is the recent appearance of test devices for cholesterol self-testing for the general public. Corporations have recognized the desire of individuals to be able to monitor health indicators outside of the physician's office and have instituted research programs to fill this need. For example, Intel Corporation has a research group devoted to home healthcare that develops products for wellness, nutrition fitness, and mental health, as well as disease management. As will be described later in this report, health maintenance is an important issue for the Japanese.

Another driver for the development of biosensing systems is the need for new and expanded technologies for monitoring and controlling the environment. In addition to a long-standing concern to identify toxic materials in the environment, in recent years, recognition of the fragility of the environment and growth of the "green" movement worldwide have expanded so rapidly that robust and diverse environmental sensing technologies have become essential to achieving social goals. In addition to the need for selectivity and sensitivity in environmental sensors, two other requirements are for robustness to allow the systems to be fielded in remote locations and for methods for relaying information to monitoring centers (see, for example, the website of the Center for Embedded Network Systems at UCLA, cens.ucla.edu/).

Further, after the 9/11 tragedy, there has been a leap in interest in sensing for security and surveillance—sensing technologies capable of identifying chemical or biological materials that can result in diseases or death. All sorts of deployments are being considered to cover the immense range of threats, from immediate poisons such as sarin to biological agents such as smallpox that may take weeks or months to incubate.

ENABLERS OF BIOSENSING TECHNOLOGIES

The increasing sophistication of biosensing technologies has become possible because of national investments in other technologies, notably fabrication methods for integrated circuits; photonics and fiberoptics; and biotechnology, particularly genetic engineering. More and more, these technology fronts are coinciding, so that one sees programs called "Bio-Nano-Info" for biotechnology, nanotechnology, and information technology. An example of the coordinated thinking along these lines was highlighted in a 2002–2003 conference and report sponsored by the National Science Foundation and the Department of Commerce entitled "Converging Technologies for Improving Human Performance: Nanotechnology, Biotechnology, Information Technology and Cognitive Science" (Roco and Bainbridge 2003).

One can see the results of this confluence of technologies as related to biosensing in the field of clinical analytical chemistry (Figure 1.3). Several decades ago, the first breakthrough in analytical procedures was the development of the "Autoanalyser" by Technicon Corporation, shown on the left of the figure. This laboratory bench device allowed the robotic processing of many samples and could be "programmed" for different assays. Later, portable versions of the chemical laboratory were developed to bring the chemistry to the workplace (such as the surgery suite), rather than bringing the samples to the chemistry laboratory. In the past decade, "point-of-care" technologies have developed to the point where tests are accomplished at the patient's bedside, so that a physician can obtain critical information while examining the patient. In the example shown, the handheld i-STAT system on the right (www.istat.com/products) provides 6 different analyses from a drop of blood in about one minute.

Further miniaturization has occurred in the last five years, resulting in commercial products where the sensor elements have been made even smaller, on the order of millimeters in size, as shown in Figure 1.4. This is a glucose sensor 1 mm in diameter under development by Medtronic/ MiniMed Corp. (www.minimed.com/) for the continuous measurement of glucose subcutaneously.

As will be seen in the technology chapters of this report, the trends toward multianalyte and miniaturized sensors have produced array-type technologies where the active elements features are on the order of microns in size, allowing for thousands of target molecules (e.g., DNA sequences, RNA sequences, proteins) to be displayed simultaneously on chips only a few square centimeters in area. The identification of materials is obtained by binding patterns that are visualized by tags of fluorescent molecules (see Figure 1.5).

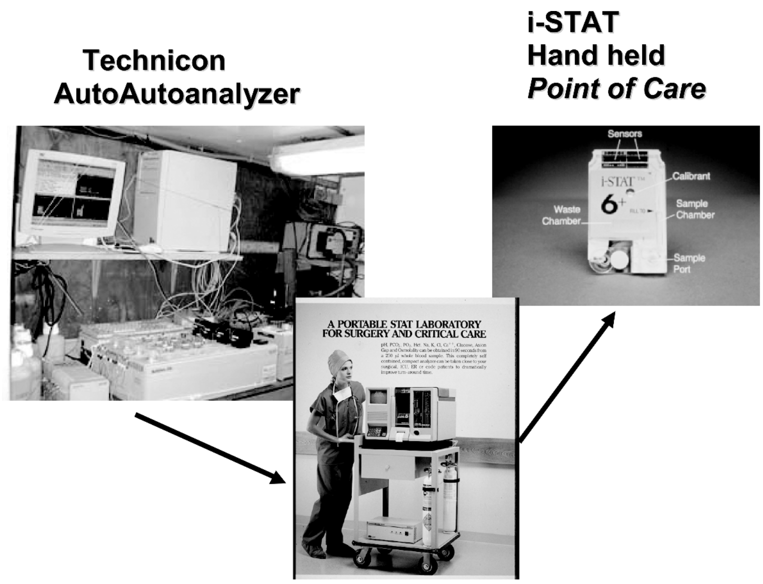

Fig. 1.3. Evolutions of the confluence of technologies as related to biosensing in the field of clinical analytical chemistry; examples from Technicon and Abbott Labs/i-STAT Corp.

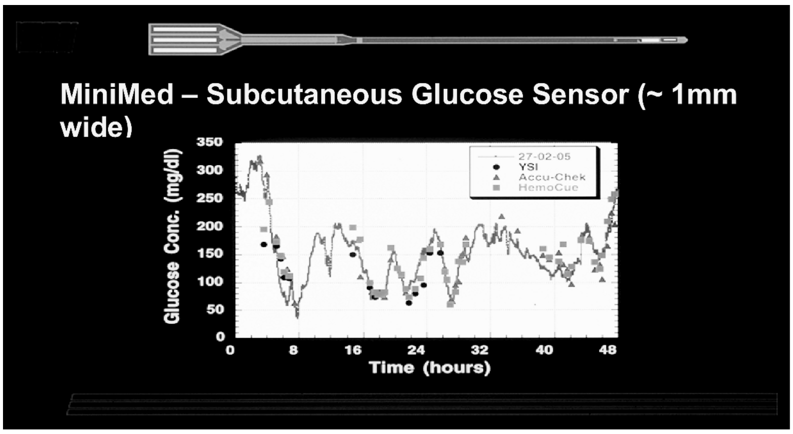

Fig. 1.4. Subcutaneous glucose sensor 1 mm wide under development by Medtronic/MiniMed Corp.

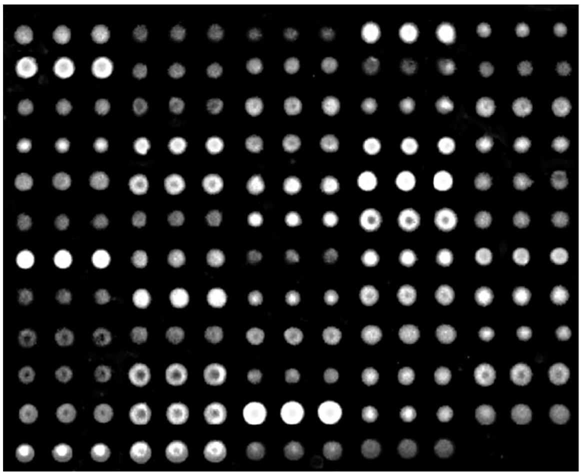

Fig. 1.5. Fluorescence pattern on an array chip for identifying DNA fragments.

BIOSENSING INFRASTRUCTURE / INVESTMENT TRENDS IN THE UNITED STATES

The WTEC biosensing panel observed that in the United States, Europe, and Japan, the strategies for investing in the creation of physical and human resources to support research—roughly defined here as "infrastructure"—played a critical role in the growth of the biosensing field in each of the regions. These strategies have guided each region in setting its government policies, seeking public funding, establishing research priorities, and putting the research results into commercial use. The panel has attempted to broadly identify and compare the infrastructure/investment circumstances in the United States, Europe, and Japan.

International marketing consulting and training firm Frost and Sullivan (2002) has made an analysis of biosensing trends in the United States and overseas, noting that the current analytical laboratory instrumentation market is about $10 billion per year, providing a great market opportunity for new biochip developments.

One only needs to note the U.S. companies that have significant development programs in genomics, proteomics, and other diagnostics to realize the significance of commercial investment in these technologies. Examples include Aclara, Affymetrix, Applied Biosystems, Beckman Instruments, Caliper, Cepheid, Curagan, Gene Logic, Genometrix, Hyseq, ID Biomedical, Incyte Pharmaceuticals, Molecular Tool, Mosaiz Technologies, Nanogen, Orchid Biocomputer, Synteni, and Vysis.

Despite the breadth of industry investment in sensing technologies and product development, much of the research funding that has enabled advanced concepts in biosensing has come from U.S. Government agencies. Although there is no comprehensive compendium of commercialization successes from this national research funding, a partial listing of some outcomes was provided at a workshop sponsored by the National Nanotechnology Initiative (NNI 2002), titled “Nanotechnology Innovation for Chemical, Biological, Radiological, and Explosive (CBRE) Detection and Protection.” This listing is reproduced in Table 1.3.

The three primary U.S. government agencies that provide funding and guide directions for development of biosensing systems and technologies are the National Institutes of Health, the National Science Foundation, and the Department of Defense. The goals of these agencies are somewhat different; however, the basic research promoted by these institutions has a great deal in common.

Table 1.3.
Potential Near-Term Nanotechnology with CBRE* Impact (Source: NNI 2002)

Investigator	Institution	Technology	Company
Baker	University of Michigan	nanostructured bio decontamination	NanoBio Corp.
Doshi	—	polymer nanofibers	eSpin
Hellinga	Duke University	tailored biosensors	Johnson & Johnson
Klabunde	Kansas State University	nanocluster agent catalysis	Nanoscale Materials
Lieber	Harvard University	nanotube sensors	Nanosys
Martin	University of Florida	nanotube membranes	Broadley-James Co.
Mirkin	Northwestern University	nanoAu biological sensing	Nanosphere
Russell	University of Pittsburgh	sensing wipe	Agentase
Smalley	Rice University	carbon nanotube (CNT) for adsorbents	CNI
Snow	Naval Research Laboratory	nanoAu chemical sensing	MicroSensor Systems
Tatarchuk	Auburn University	CNT adsorbent media	IntraMicron Inc
Thundat	Oak Ridge National Lab. (ORNL)	cantilever sensing	Protiveris
Walt	Tufts University	nanoarray sensors	Illumina

*CBRE: Related to Chemical, Biological, Radiological, and Explosives R&D and commercialization

National Institutes of Health (NIH)

As an insight into NIH's priorities in biosensing, the proceedings from a Bioengineering Consortium (BECON) conference in 2002 gave an overview of biosensing research and provided guidance for future research in this field (BECON 2002). Suggestions from that report concerning opportunities and responsibilities for future NIH funding of research programs include the following:

- translation of [state-of-the-art] technology to the clinic or laboratory
- encouragement of awareness by researchers working in sensor development concerning the impact of their choice of biological models, which can impact sensor function dramatically
- encouragement of researchers to aim for utilization of complex mixtures, such as blood or saliva, in design of sensors that will permit the measurement of chemical, biological, and physical parameters
- emphasis on real-world field validation (for rescue work, third-world inaccessible populations, public health applications, etc.)
- application of computer science to sensor research needs in areas of data acquisition, data storage, analyses of dissimilar sets of data, algorithm development, performance modeling, telehealth, and medical information systems
- support of sensor materials research and development, specifically for materials with short response times; applicability to continuous or multiple measurement; and ability to deliver drugs, sense environments, detect therapeutic efficacy, and monitor physiology
- development of noninvasive sensors by the application of imaging technologies, with a focus on improvement of co-registration methods and development of high-performance optics to enhance the depth of measurement while maintaining molecular information
- support for the creation of a database/clearinghouse for building research teams with relevant skills and knowledge
- focus on gaps and deployment barriers that exist in sensor development, including the major problem of loss of sensor function in contact with complex mixtures such as blood, saliva, or interstitial fluid

In this BECON (2002) conference report, NIH also notes that standards and protocols are required, especially prior to the stage where the technology can be tested in animals or people:

- "functional standards" should correlate to the desired phenomenon (e.g., disease presence or analyte concentration)

- systems integration should combine the inputs from several sensors to yield useful integrated information from advances in miniaturization, materials, signal transduction, drug delivery, etc.
- micro/nano systems should integrate multiple functions to achieve performance and cost advantages
- research should define methods for the manufacture and transport of cell-based biosensors that are differentially sensitive to environmental stimuli (e.g., temperature, G-forces, culture medium, barometric pressure), and it should consider the condition of the cells attached to the sensor at the final place of use
- approaches to producing quantitative data from a large array of multiplexed data should overcome the major limitations in assays/sensors due to immobilized recognition and/or transduction events at interfaces

In order to characterize current research supported by NIH, the WTEC panel undertook a search on the NIH websites of all grants awarded in calendar year 2002, using the following keywords to select projects related to biosensors: biosens*, enzyme* and sens*, electro* and sens*, saw and sens*, antibody and sens*, optic and sens*, dna and sens*, gene and sens* (asterisks represent wildcards, to pick up various word endings in the search). The list of about 200 grants is given in Appendix D. Although the newly formed National Institute for Biomedical Imaging and Bioengineering (NIBIB) has a core interest in promoting sensor-related research, it is clear that many NIH Institutes have been supporting research in this field, attesting to the importance of these technologies across all of the health sciences.

National Science Foundation

With regard to biosensing, NSF traditionally has focused its funding activities on the fundamental sciences of materials, surface science, optics, and spectroscopy. In an open letter to the scientific community dated April 16, 2002 (www.nsf.gov/pubs/2002/nsf02112/nsf02112.pdf), NSF outlined its interest in sensing relative to its decision to provide added funding for R&D for next-generation sensors, particularly in multidisciplinary efforts:

> The goal of this effort is to speed advancements in the understanding, development, and applications of sensors. Specifically, improved and more reliable materials and protocols are sought which result in higher sensitivity, fewer false alarms, wireless operation, multifunctionality (e.g., simultaneous detection of both chemical and biological species), practicality, etc. Sensing principles

include but are not limited to optical, electrochemical, electrical, acoustic, and mass sensing phenomena. Multidisciplinary efforts are encouraged. Specific research areas might include but are not limited to:

1. Synthesis and testing of new low cost materials with high sensitivity, selectivity, robustness, and speed for defined sensor applications. Materials having predictable and tunable recognition properties, as well as robustness under anticipated manufacturing schemes, are desired. Work may include modeling of material/analyte interactions and design of specific binding sites. Also of interest are biologically sensitive materials and materials with biorecognition surfaces and membranes. Packaging materials and methodologies specific to sensing applications are also of interest.

2. New approaches for achieving sensitivity, selectivity, robustness, low cost and high speed for defined sensor applications. These might include but are not limited to: (a) development of biologically-motivated amplification schemes and sensing principles, (b) development of label-free assays for various pathogens (including recognition schemes for surface proteins, glycoproteins and other surface markers for rapid detection of pathogens), and development of functionally defined selectivity (e.g., neurotoxicity). Exploration of the dynamic behavior of sensors for various applications is another possible research area.

3. New approaches for the integration of diverse sensor data, including homogeneous arrays, higher order arrays, and superarrays. Development of new statistical algorithms and sampling theories tailored to specific sensor applications.

4. New approaches leading to miniaturization strategies, including lab-on-a-chip projects and power and vacuum pumping capabilities (for miniaturization of mass spectrometers or chromatographs, for example).

It should be noted that besides providing support specifically for sensing R&D, NSF also supports numerous programs in technologies that contribute both directly and indirectly to advancement of sensing technologies (the bio-nano-info connections). In addition to research grants, NSF also supports equipment facilities, workshops, educational programs, and small business grants.

The WTEC panel searched all grants awarded by NSF during 2002 for indications of programs with a focus on or application to sensing. The results were acquired from the Fielded Search (full text) on the NSF Awards website, using the keywords biosens*, enzyme* and sens*, electro* and sens*, saw and sens*, antibody and sens*, optic and sens*,dna and sens*, gene and sens*.The result was a compilation of about 400 awards; the results were then screened and approximately one-half discarded because they obviously were not related to biosensing. The ~200 NSF awards related to biosensing are listed in Appendix E.

Department of Defense

Although the Department of Defense (DOD) had been supporting programs in sensing technologies for a number of years through the Defense Advanced Research Projects Agency (DARPA), its efforts accelerated dramatically following 9/11/2001. In February of 2003, the Department of Defense released its *Fiscal Year (FY) 2004/FY 2005 Biennial Budget Estimates*. The following information is from that estimated budget document, specifically Volume 1 describing DARPA projects (DARPA 2003).

In the approximately $2.8 billion planned budget for DARPA's Research, Development, Test, and Evaluation Program in Fiscal Year 2004, about $291 million was allocated in programs that relate to biosensing. These programs are titled "Defense Research Sciences" (Program Element 0601101E) and Biological Warfare Defense (Program Element 0602383E). These programs consist of several sub-elements, including the programs BioComputational Systems; Simulation of Bio-Molecular Microsystems (SIMBIOSYS); Nanostructure in Biology; and Molecular Observation, Spectroscopy, and Imaging using Cantilevers (MOSIAC) program, all of which impact sensing research. There is a clear focus in several of these programs on multidisciplinary integration and exploration of phenomena at the nanoscale. Outlines of DARPA programs are given in Appendix F, taken from the published estimated budget information.

The focus of the DARPA-funded research is on DOD issues and products such as design of novel materials; sensing and computational devices or dynamic biological materials that utilize or mimic biological elements for force protection and medical intervention; new leads for the development of threat countermeasures; and improvement of human performance. Nevertheless, it is clear from DARPA statements in the estimated budget document that it planned to support a great deal of fundamental research at the interface between biology, materials, and information sciences, in order to "develop the basic research tools in biology that are unique to the application of biological based solutions to critical Defense problems" (DARPA 2003). The outcomes of these research projects will undoubtedly find applications in the public and private sectors, in keeping with the philosophy of "dual-use" now being promoted by many government agencies.

DARPA "Defense Research Sciences" and "Biological Warfare Defense" projects probably constitute the major sources of DOD support for biosensing research, but there are other agencies that actively support these kinds of activities as well. For example, the U.S. Army Corps of Engineers issued a solicitation for "Sensor Systems, Data Acquisition, Processing, and Transmission Systems" in support of military engineering, civil engineering, environmental engineering, and homeland defense. The Army Research Office has shared with WTEC a list compiled in March 2004 of about 50 active projects related to biosensing research for chemical and biological warfare defense; these are presented in Appendix G.

Programs at U.S. Government Laboratories

With the exception of NIH, the U.S. government agencies discussed above are primarily funding agencies that direct research by their funding priorities. In addition, there are several U.S. Government laboratories that perform extensive research and development programs in biosensing systems. The Naval Research Laboratory in Washington, D.C., has been particularly successful in taking biosensors from an initial concept to on-site application (www.nrlbio.nrl.navy.mil/, www.chemistry.nrl.navy.mil/). At least six biosensors invented at NRL are commercially available for uses including detection of drugs of abuse, explosives, pathogens in foods, bioterrorism agents, and research targets, with more biosensor technologies currently under commercialization. NASA (www.NASA.gov) also has a number of research programs related to biomedical and environmental sensing technologies at its various centers, including the Jet Propulsion Laboratory, Ames Research Center, and Johnson Space Center. The Army has also had a long-standing biosensor development and testing effort at Soldier Biological and Chemical Defense Command exploring military applications for biosensors and adapting them for field use.

One of the larger efforts is being undertaken by the Department of Energy, where the Office of Science devotes about $1.5 billion per year to programs in Basic Energy Sciences and Biological and Environmental Research. About one-third of these funds go to universities and the remainder to in-house projects. Although a breakdown relating to sensing research is not available, in 1999 DOE published an inventory of research conducted in its national laboratories that related to biomedical engineering research (www.osti.gov/sc73/doe-sc-1999-1.pdf). From that document, the WTEC panel identified and tabulated DOE projects that relate to biosensing systems; these are presented in Appendix H. They amounted to about 50 biosensing-related projects in 10 different DOE facilities. This represents a large amount of research sponsored by a single agency, however, the fact that the work is broadly distributed may limit its impact compared to some of the integrated research programs that the panel observed in Europe.

BIOSENSING INFRASTRUCTURE/INVESTMENT TRENDS IN EUROPE

A great deal of insight into biosensing research in Europe can be obtained from the research programs sponsored by the European Union (EU). During the WTEC panel's visits to various European research laboratories, we were informed that EU funding usually amounted to about 15% of a laboratory's total funding. However, the general scope of priorities as outlined in EU news articles and public documents provides a reasonable view into the interests and directions for future European research. Several of these are surveyed below.

Some general observations relating to biosensor R&D in Europe were reported in an article, "Biomedical Applications of Nanotechnology," by Ineke Malsch (2002). The article reported that the European Commission, which finances about one-quarter of the publicly funded research in the EU, was to spend about $300 million on nanotechnology projects in 2003, as compared to $700 million for the National Nanotechnology Initiative (NNI) budget in the United States. A portion of the European funds will go to biomedical applications that include diagnostics and biosensing technologies. Malsch noted that the focus of Europe's government nanotechnology R&D is on relatively short-term product development and is collaborative (Malsch 2002):

> In Europe, public research funding and networking for nanotechnology in industry tend to be more focused on applications with a time-to-market of 5 to 10 years. The international Network for Biomedical Applications of Micro & Nano Technologies (NANOMED), based in Newcastle upon Tyne (U.K.), has brought together 50 industrial and academic partners to develop bio medical applications of nanotechnology. In Germany, the Nanochem network, based at the University of Kaiserslautern, is organized in a similar public-private fashion and includes medical applications of nanotechnology. Germany has had by far the highest

> budget for nanotechnology research in Europe for several years; in 2000, funding was at a level of $56.7 million.

Malsch's article, which supports the WTEC team's observation of the emphasis in European biosensing R&D on public-private collaboration, gives this example:

> The Micro Electronics Material Engineering Sensors and Actuators (MESA+) research institute at the University of Twente (Enschede, The Netherlands) is engaged in high-throughput screening (HTS) research for Avantium in Amsterdam, an R&D company founded in 2000 by a consortium of chemical and pharmaceutical companies, venture capitalists, and three Dutch universities. Avantium aims to develop new strategies and equipment for screening active compounds for pharmaceutical and other products—specifically through development of highly sophisticated lab-on-a-chip systems.

For a more comprehensive view of public funding for science and technology research in the European Union, Table 1.4 gives an overview of the EU Sixth Framework Programme. The budget estimates are for the period 2002–2006. The actual implementation of this program is rather complex, and the reader is referred to the website www.cordis.lu/fp6/ for more detailed information.

An examination of the specific goals of the eight major research program elements reveals that there will be significant support for biosensing research in Elements 1, 2, 3 (and 5). General outlines for these programs follow; more details of the EU Sixth Framework Programme program objectives and research activities related to biosensing are given in Appendix I.

1. Life sciences, genomics, and biotechnology for health
   - Genomics and biotechnology for health
   - Advanced genomics and its application for health
   - Fundamental knowledge and basic tools for functional genomics in all organisms: gene expression and proteomics, structural genomics, bioinformatics, etc.
   - Application of knowledge and technologies in genomics and biotechnology for health: technological platforms, prevention, and therapeutic tools, etc.
   - Combating major diseases

Table 1.4.
EU Sixth Framework Programme, Research Budget

Thematic Priorities	€ million*
1. Life sciences, genomics and biotechnology for health	2,255
Advanced genomics and its applications for health	1,100
Combating major diseases	1,155
2. Information Society technologies	3,625
3. Nanotechnologies and nano-sciences, knowledge-based multifunctional materials, and new production processes and devices	1,300
4. Aeronautics and space	1,075
5. Food quality and safety	685
6. Sustainable development, global change, and ecosystems	2,120
Sustainable energy systems	810
Sustainable surface transport	610
Global change and ecosystems	700
7. Citizens and governance in a knowledge-based society	225
8. Specific activities covering a wider field of research	1, 300
Total	†**13,345**

* Conversion is approximately €1.00 = US$1.25; inverse, 0.80 (Dec. 2003).
† Including non-nuclear activities of the Joint Research Centre: €760 million.

- Application-oriented genomic approaches to medical knowledge and technologies: diabetes, cardiovascular diseases, resistance to antibiotics, brain, and ageing, etc.
- Cancer
- Major poverty-linked infectious diseases: aids, malaria, and tuberculosis

2. Information society technologies (IST)
   - Applied IST research addressing major societal and economic challenges: security, societal challenges, “ambient intelligence,” electronic commerce, etc.
   - Communication, computing, and software technologies
   - Components and microsystems
   - Knowledge and interface technologies
3. Nanotechnologies and nanosciences, knowledge-based multifunctional materials, and new production processes and devices

- Nanotechnologies and nanosciences: long-term research, supramolecular architectures and macromolecules, nano-biotechnologies, applications in health, chemistry, etc.
- Knowledge-based multifunctional materials: fundamental knowledge; production, transformation and processing technologies, etc.
- New production processes and devices: flexible and intelligent manufacturing systems, systems research and hazard control, clean and safe production, optimisation of life cycles, etc.

Within the patterns of European Union R&D funding, there is a strong emphasis on building collaborative research centers that span country lines. As an example, during the Fifth EU program cycle, Cranfield University in the UK organized the research consortium SENSPOL (www.cranfield.ac.uk/biotech/senspol/). For the current Sixth Programme, Cranfield has expanded this effort and is in the process of developing a Network of Excellence in Sensing Technology (NEST), comprised of 120 biosensor labs selected from over 4,000 sensor labs in 24 countries. There are over 100 people at Cranfield working in this sensor network.

The WTEC panel observed firsthand a general pattern in Europe for the formation of integrated networks for enhancing research and technology, particularly with the goal of business generation. An excellent example of this trend is the growth of the biotechnology/biomedical capability in the Berlin-Brandenburg region of Germany. Three Max Planck Institutes and two Fraunhofer Institutes are located on the campus of the University of Potsdam, in addition to the University's own institutes. The focus of much of the science in these institutes is biotechnology and life sciences. A number of private companies are already emerging from this scientific synergy. The local political establishment is highly supportive of the region's focus on biotechnology, helping to fund infrastructure development, including several interdisciplinary technology parks. It also helps to coordinate biotechnology activities via a central office, BioTOP Berlin-Brandenberg, which among other functions hosts the BioTOP web site (www.biotop.de/index_e.asp?main=3) and produces the BioTOPics newsletter (e.g., see www.biotop.de/download/BraRep_eng.pdf, May 2002). The charts below, Figures 1.6 and 1.7, accessed from the *BioTOP* website, show the growth of the biotechnology industry in this region, and the product areas for these companies. At the writing of this report, over 100 companies in the Berlin-Brandenburg region have activities in diagnostics, instruments, or software that have some relationship to biosensing systems and technologies.

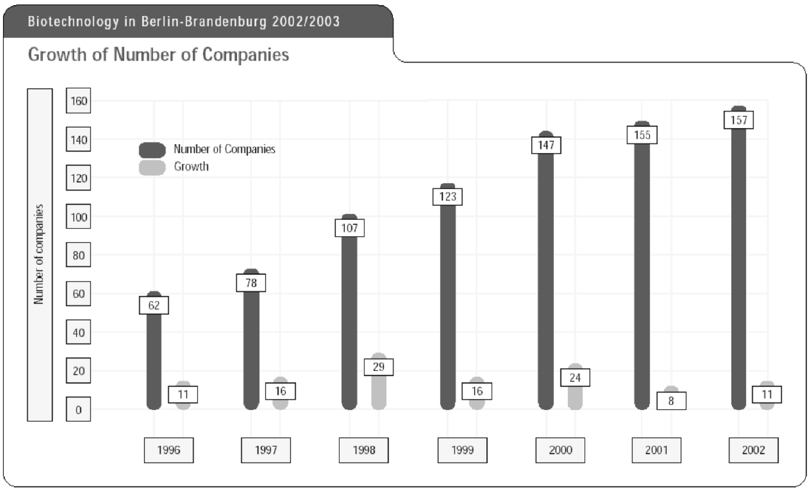

Fig. 1.6. Growth of the biotechnology industry in Berlin-Brandenburg region. (Source: BioTOP Biotech Report May 2003, available online www.biotop.de/download/Biotech_Report_02_03_en.pdf)

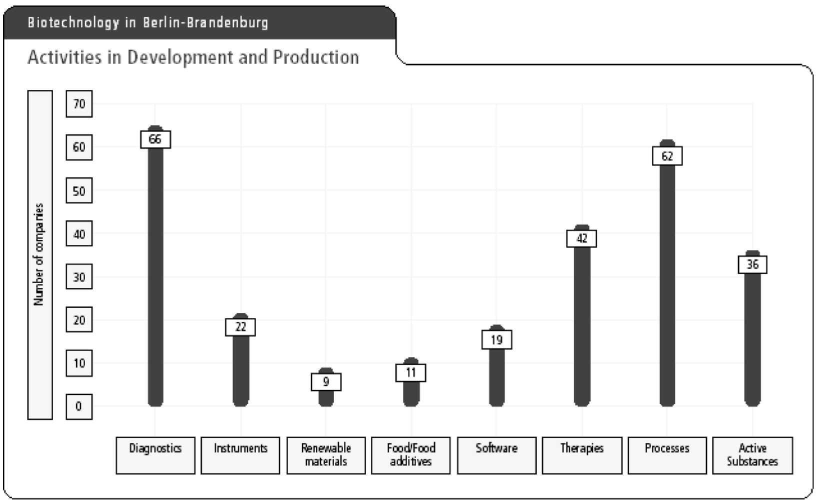

Fig. 1.7. Product areas for the biotechnology industry in Berlin-Brandenburg region. (Source: BioTOPics May 2002; www.biotop.de/download/BraRep_eng.pdf)

The WTEC panel conducted a survey of the patent literature for the sites that it visited in Europe in order to gain some appreciation for the range of commercialization activities for those centers that are involved in biosensing research. The results, tabulated in Table J.1 in Appendix J, indicate a significant effort in obtaining patents on the part of many university laboratories across Europe.

BIOSENSING INFRASTRUCTURE/INVESTMENT TRENDS IN JAPAN

Sites the WTEC panel visited in Japan included universities, government research laboratories, and companies. A common and important feature of these visits was the major change in attitude towards cooperative ventures between all these types of institutions for new product development. The panel's visit to the Tokyo University of Agriculture and Technology (TUAT) was indicative of this trend.

In TUAT's 2002 informational brochure (TUAT 2002), President Dr. Seizo Miyata is quoted as follows:

> For the sustainable development of the country, research in the following four fields will be of great significance in the 21st century:
>
> 1) Biotechnology, which will assist in the prevention and treatment of disease and help in solving future food problems;
>
> 2) Information and Communications Technologies, represented primarily by computers, cell phones and the Internet;
>
> 3) Environmental Science and Resource Science, which are essential to the survival of human kind;
>
> 4) Nano-technology (nanometer scale manufacturing technology) and research on new materials, which will have immense influences on our daily lives.

TUAT information also notes that patents jumped from 12 in 1999 to 136 in 2002 in the Graduate School of Bio-Applications and Systems Engineering, and that 116 cooperative research projects were carried out in 2002 by about 450 faculty and research associates. The School's major fields include Dynamics of Molecular Systems; Bio-modeled Sensory Systems; Molecular Mechanism of Bio-Interaction; and Biological and Environmental Sensing Systems.

With support from the Ministry of Education, TUAT has actively promoted cooperative ventures with private researchers since 1988, and it started providing advanced facilities for joint research in its Cooperative Research Center in 1989. The Center was expanded in 1996, and in 2001 it added a liaison office to better promote commercialization activities. The photograph in Figure 1.8 of the Cooperative Research Center building indicates the level of commitment to facilitating university-industry technology transference.

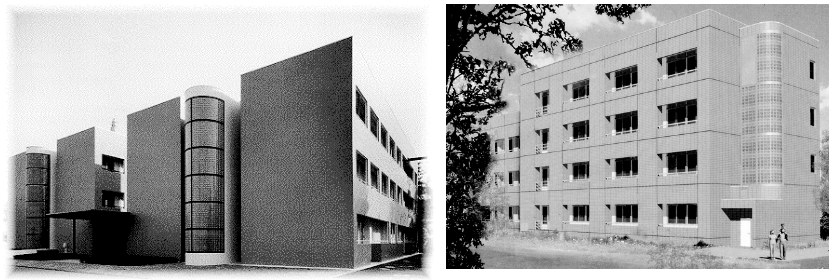

Fig. 1.8. Cooperative Research Center at TUAT.

Another example of the trend for the direct connection of university and corporate research is the new School of Bionics at Tokyo University of Technology . A new US$250 million building with 15,000 m^2 of space, pictured in Figure 1.9, opened in 2003 to house industrial/academic research projects, along with the traditional research and academic facilities. About twenty new faculty have been hired for a new bionics program led by Prof. Isao Karube, which is housed in this building, called Katayanagi Advanced Research Laboratories. Four floors of the new facility are occupied by corporate research laboratories that co-sponsor research in the institute. The university is building a degree program in technology management.

A similar emphasis on collaboration is also evident at RIKEN, one of Japan's premier national research institutes, as described by the Director of the Frontier Research System (FRS) (RIKEN 2002), Dr. Eiichi Maruyama. Dr. Maruyama noted that RIKEN's Frontier Research Program (FRP), in existence from 1986–1997, initiated an experimental research system consisting of fixed-term contract researchers that "introduced dynamism into Japanese research system and achieved remarkable research results." The FRP was succeeded in 1997 by the Brain Science Institute and then by the present Frontier Research System in 1999, with a more diverse project orientation towards novel, world-class basic scientific research, but maintaining FRP's organizational focus on bringing together "high caliber scientists from different disciplines to work together on cutting edge research projects…and to continue to develop and incubate novel interdisciplinary research areas" (RIKEN 2002).

Fig. 1.9. Tokyo University of Technology's Katayanagi Advanced Research Laboratories building, which houses the Bio-nanotechnology Center, Content Technology Center, Advanced IT Center, Creative Lab, Encoding Center, and Bionics Research Center, which is part of the academia-government-industry Collaborative Research Center.

FRS apparently is regarded as a unique approach by Japan's government to expand scientific knowledge via national and international scientific cooperation and project management that is flexible with regard to duration of projects; composition of research teams (including active recruitment of creative young researchers both within Japan and overseas); and involvement by international as well as national experts. Buoyed by successes in its predecessor programs, RIKEN is dedicated to fostering dynamic and flexible management in FRS, with the goals of creating new fields in science/technology, to benefit industry, the economy, and society at large.

These observations on changes in programs as related to new technologies were echoed in an article by Jean-Francois Tremblay, "Unleashing R&D in Japan," that appeared December 2002 in *Chemical and Engineering News* (pubs.acs.org/cen/topstory/8049/8049bus1.html). Tremblay describes several initiatives within Japanese funding agencies that are designed to increase funding to and economic benefit from R&D activities in universities and national research laboratories, especially in terms of increasing emphasis on patenting innovations and on transferring innovation from the laboratory to industry. These changes are reflected in the "new" National Institute of Advanced Industrial Science and Technology (AIST), which in 2001 grew out of a merger between 15 institutes run by the "old AIST" (the Agency of Industrial Science and Technology), and the Weights and Measures Training Institute, becoming the nation's largest public research organization (Tremblay 2002):

> The 3,200 scientists at AIST are now urged to conduct research that can be of use to industry, according to Takashi Goto, director of AIST's collaboration department. It's a 180- degree turn, he says, from the situation at the old AIST, which emphasized basic research.
>
> At the old AIST, Goto relates, researchers were primarily evaluated on the quality and quantity of their published research. Under the new system, "if a researcher does not publish particularly outstanding papers but comes up with useful patentable research, it will be looked upon very favorably." He adds that basic science is not dead at AIST. "Researchers can still go on simply publishing papers; it's just that there is another dimension to the way that they are evaluated," he says.
>
> Although the change occurred only one-and-a-half years ago, collaboration with private companies or universities is expanding rapidly. In 2000, the last year of the old AIST, 972 research projects were conducted with outside groups. In 2001, this had already grown to 1,131 projects. An additional dimension to the improvement, Goto says, is that several joint research projects now extend over several fiscal years, a type of arrangement that was prohibited at the old AIST.
>
> AIST also made a number of administrative changes to help technology transfer to private companies. The old AIST did not have a collaboration department, a technology licensing office, or even a patent policy office. Whereas before AIST researchers were not allowed to collect licensing fees exceeding $46,000, there is now no absolute limit on how much they can earn from their licenses—as long as AIST gets 75% of the proceeds.

Shin-ichi Kamei of Mitsubishi Research Institute in reviewing Japan's strategy for nanotechnology and its competitive position relative to the United States indicates that one of Japan's programs will be "nanotechnologies for observing the phenomena of biocompatible organisms and utilizing or controlling their mechanisms." Hideki Shirakawa, who won a Nobel Prize for chemistry in 2000, will head a nanotechnology effort. It appears that approximately $600 million of government funds will be allocated for this effort. An outline of Japan's research strategy is given in the government document, "The Science and

Technology Basic Plan, 2001–2005" (www8.cao.go.jp/cstp/english/basicplan01-05.pdf). Some Japanese companies are establishing partnerships with American universities, e.g., Fujitsu and the University of Maryland (pr.fujitsu.com/en/news/2001/02/26.html).

The increased emphasis on product development in Japan has resulted in a major increase in patent applications, especially from university faculty. Table J.2 in Appendix J lists the patents related to biosensing obtained from 1999 through February 2003 by the Japanese institutions visited in this WTEC study.

As a complement to this overview of relative organizational and funding patterns of the United States, Europe, and Japan in the fields of biosensing research and development, a bibliometric study of international biosensors research is included in Appendix K that underscores the growing activity in this area of all three regions, based on the number and quality of published biosensor studies in the period 1997–2002. (There is some insight, as well, into the interest in biosensing R&D in other countries not included in the WTEC study.)

SUMMARY

Several key factors may be used to provide a guide for assessing the relative approaches and strengths of infrastructure development in biosensing research: networking and consortia, product development, technology transfer, company development, and national priorities. Table 1.5 shows what drives each of these factors, how they are implemented, and the relative strengths of the three regions. Briefly, the WTEC panel finds that Europe is the trendsetter in developing networked consortia, both local and international, for interdisciplinary R&D. Europe and Japan are very active in university–industry collaboration for product development; Japan in particular is placing strong emphasis on technology transfer through newly enacted laws and funding policies. For company development, with its unique venture capital environment, the United States leads and will continue to lead in this area. Finally, the United States leads in setting national priorities and coupling them to biosensing research and related work.

Table 1.5.
Comparison of Infrastructure Development in Biosensing R&D: U.S., Europe, and Japan

Topic	Drivers	Implementation	Trend Leaders
Networking and Consortia	National/regional policy	Joint funding	Europe United States Japan
Product Development	National policy University policy Corporate	Faculty participation in companies	Europe Japan United States
Technology Transfer	National policy University policy	Accelerated patent procedures	Japan Europe United States
Company Development	Venture capital University policy	SBIR type programs	United States Europe Japan
National Priorities	Health Environment Security	Selected funding	United States Europe Japan

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