

# **SIGNIFICANT ITEMS (SIs)**

## **FY 2011 Senate Appropriations Committee Report**

### Table of Contents

|                                                                            |     |
|----------------------------------------------------------------------------|-----|
| NATIONAL CANCER INSTITUTE.....                                             | 7   |
| NATIONAL HEART, LUNG, AND BLOOD INSTITUTE .....                            | 24  |
| NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH .....               | 33  |
| NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES .....     | 37  |
| NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE .....              | 47  |
| NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES .....                | 58  |
| NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES .....                       | 69  |
| NATIONAL INSTITUTE OF CHILD HEALTH & HUMAN DEVELOPMENT .....               | 70  |
| NATIONAL EYE INSTITUTE .....                                               | 84  |
| NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES .....                  | 86  |
| NATIONAL INSTITUTE ON AGING .....                                          | 92  |
| NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASE ..... | 97  |
| NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATIONS DISORDERS .....    | 103 |
| NATIONAL INSTITUTE OF MENTAL HEALTH .....                                  | 113 |
| NATIONAL INSTITUTE ON DRUG ABUSE.....                                      | 117 |
| NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM .....                   | 129 |
| NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING .....          | 131 |
| NATIONAL CENTER FOR RESEARCH RESOURCES .....                               | 133 |
| NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES .....         | 136 |
| FOGARTY INTERNATIONAL CENTER .....                                         | 137 |
| NATIONAL LIBRARY OF MEDICINE .....                                         | 139 |
| OFFICE OF THE DIRECTOR .....                                               | 144 |

## **A**

|                                                 |            |
|-------------------------------------------------|------------|
| <b>Access to Research Information .....</b>     | <b>139</b> |
| <b>Adolescents.....</b>                         | <b>7</b>   |
| <b>Adverse Pregnancy Outcome .....</b>          | <b>70</b>  |
| <b>Age-related Bone Loss .....</b>              | <b>92</b>  |
| <b>Alternative Methods of Testing .....</b>     | <b>86</b>  |
| <b>Amyotrophic Lateral Sclerosis (ALS).....</b> | <b>144</b> |
| <b>Angiogenesis.....</b>                        | <b>24</b>  |
| <b>Autoimmune Diseases.....</b>                 | <b>145</b> |

## **B**

|                                                       |            |
|-------------------------------------------------------|------------|
| <b>Basic Behavioral and Social Sciences .....</b>     | <b>146</b> |
| <b>Basic Cell Research .....</b>                      | <b>147</b> |
| <b>Behavioral Economics .....</b>                     | <b>93</b>  |
| <b>Behavioral Genetics .....</b>                      | <b>117</b> |
| <b>Behavioral Management Drugs for Children .....</b> | <b>114</b> |
| <b>Behavioral Neuroscience .....</b>                  | <b>71</b>  |
| <b>Behavioral Research on Tobacco Control .....</b>   | <b>8</b>   |
| <b>Behavioral Research Training- .....</b>            | <b>69</b>  |
| <b>Bone defects .....</b>                             | <b>9</b>   |
| <b>Bone Disease .....</b>                             | <b>131</b> |
| <b>Bone Loss .....</b>                                | <b>97</b>  |
| <b>Breast Cancer Surveillance-.....</b>               | <b>10</b>  |

## **C**

|                                                                      |            |
|----------------------------------------------------------------------|------------|
| <b>Career Development Awards .....</b>                               | <b>148</b> |
| <b>Cataracts .....</b>                                               | <b>84</b>  |
| <b>Charcot-Marie-Tooth (CMT) .....</b>                               | <b>47</b>  |
| <b>Children's Mental Health .....</b>                                | <b>113</b> |
| <b>Chimpanzee Breeding .....</b>                                     | <b>133</b> |
| <b>Chromosome Abnormalities .....</b>                                | <b>72</b>  |
| <b>Chronic Fatigue .....</b>                                         | <b>22</b>  |
| <b>Chronic Hepatitis B .....</b>                                     | <b>58</b>  |
| <b>Chronic Kidney Disease (CKD) and Asian/Pacific Islanders.....</b> | <b>37</b>  |
| <b>Class B Animal Dealers .....</b>                                  | <b>149</b> |
| <b>Clinical and Translational Science Awards (CTSAs) .....</b>       | <b>149</b> |
| <b>Clinical Trials Network.....</b>                                  | <b>12</b>  |
| <b>Collaboration With State Substance Abuse Agencies .....</b>       | <b>129</b> |
| <b>Communication of Research Findings .....</b>                      | <b>150</b> |
| <b>Comorbidity .....</b>                                             | <b>129</b> |
| <b>Comparative Effectiveness .....</b>                               | <b>118</b> |
| <b>Congenital Heart Disease .....</b>                                | <b>25</b>  |
| <b>Contraceptive Research and Development .....</b>                  | <b>73</b>  |

|                                    |           |
|------------------------------------|-----------|
| <b>Craniofacial Skeleton .....</b> | <b>34</b> |
|------------------------------------|-----------|

## **D**

|                                                |            |
|------------------------------------------------|------------|
| <b>Demographic and Economic Research.....</b>  | <b>94</b>  |
| <b>Demographic Research .....</b>              | <b>74</b>  |
| <b>Diabetes .....</b>                          | <b>151</b> |
| <b>Diamond-Blackfan Anemia (DBA).....</b>      | <b>26</b>  |
| <b>Disaster Information Management .....</b>   | <b>140</b> |
| <b>Dissemination of Research Results .....</b> | <b>115</b> |
| <b>Down Syndrome .....</b>                     | <b>153</b> |
| <b>Dystonia Consortium .....</b>               | <b>154</b> |

## **E**

|                                               |            |
|-----------------------------------------------|------------|
| <b>Early Detection and Intervention .....</b> | <b>103</b> |
| <b>Endocrine Disruption .....</b>             | <b>87</b>  |
| <b>Engaging the Medical Community .....</b>   | <b>119</b> |
| <b>Eosinophil-associated Disorders .....</b>  | <b>59</b>  |
| <b>Epidermolysis Bullosa (EB) .....</b>       | <b>98</b>  |
| <b>Epilepsy .....</b>                         | <b>48</b>  |

## **F**

|                                      |            |
|--------------------------------------|------------|
| <b>Fibromyalgia.....</b>             | <b>155</b> |
| <b>Fragile X Syndrome .....</b>      | <b>75</b>  |
| <b>Frontotemporal Dementia .....</b> | <b>49</b>  |
| <b>Funding Needs .....</b>           | <b>141</b> |

## **G**

|                                                                     |            |
|---------------------------------------------------------------------|------------|
| <b>Gastric cancer .....</b>                                         | <b>13</b>  |
| <b>Global Health Research Training and Workforce Capacity .....</b> | <b>137</b> |
| <b>Glomerular Disease Research .....</b>                            | <b>38</b>  |

## **H**

|                                                        |            |
|--------------------------------------------------------|------------|
| <b>Hair Cell Regeneration .....</b>                    | <b>104</b> |
| <b>Health Disparities Research in Women.....</b>       | <b>156</b> |
| <b>Hearing Aids and Cochlear Implants .....</b>        | <b>105</b> |
| <b>Heart Disease .....</b>                             | <b>27</b>  |
| <b>Hematology (Regenerative Medicine) .....</b>        | <b>175</b> |
| <b>HIV/AIDS and Criminal Justice Populations .....</b> | <b>120</b> |
| <b>HIV/AIDS Behavioral Research .....</b>              | <b>157</b> |
| <b>Human Tissue Supply.....</b>                        | <b>134</b> |

## **I**

|                                                                                    |              |
|------------------------------------------------------------------------------------|--------------|
| <b>Immigrant Health</b> .....                                                      | <b>115</b>   |
| <b>Inflammatory Bowel Disease (IBD)</b> .....                                      | <b>39,60</b> |
| <b>Inflammatory Digestive Diseases in Children</b> .....                           | <b>40</b>    |
| <b>Intellectual and Developmental Disabilities Research Centers (IDDRCs)</b> ..... | <b>76</b>    |
| <b>Interstitial Cystitis (IC)</b> .....                                            | <b>41</b>    |
| <b>Irritable Bowel Syndrome (IBS)</b> .....                                        | <b>42</b>    |

## **L**

|                                                       |            |
|-------------------------------------------------------|------------|
| <b>Leber Congenital Amaurosis</b> .....               | <b>84</b>  |
| <b>Liver cancer</b> .....                             | <b>14</b>  |
| <b>Lung cancer</b> .....                              | <b>15</b>  |
| <b>Lung Disease</b> .....                             | <b>159</b> |
| <b>Lupus</b> .....                                    | <b>158</b> |
| <b>Lyme Disease</b> .....                             | <b>160</b> |
| <b>Lymphatic Research and Lymphatic Disease</b> ..... | <b>161</b> |

## **M**

|                                                               |              |
|---------------------------------------------------------------|--------------|
| <b>Marfan Syndrome</b> .....                                  | <b>28,99</b> |
| <b>Maternal Fetal Medicine Units Network</b> .....            | <b>77</b>    |
| <b>Medications Development</b> .....                          | <b>121</b>   |
| <b>Melanoma</b> .....                                         | <b>16</b>    |
| <b>Metabolic Disease and Bone Health</b> .....                | <b>78</b>    |
| <b>Microbicides</b> .....                                     | <b>61</b>    |
| <b>Military Personnel, Veterans, and Their Families</b> ..... | <b>122</b>   |
| <b>Mitochondrial Disease and Dysfunction</b> .....            | <b>163</b>   |

## **N**

|                                                                    |            |
|--------------------------------------------------------------------|------------|
| <b>Nanoparticles</b> .....                                         | <b>18</b>  |
| <b>National Children's Study</b> .....                             | <b>164</b> |
| <b>National Commission on Digestive Disease</b> .....              | <b>42</b>  |
| <b>Neglected Tropical Diseases</b> .....                           | <b>63</b>  |
| <b>Neuroblastoma</b> .....                                         | <b>19</b>  |
| <b>Neurodegeneration with Brain Iron Accumulation (NBIA)</b> ..... | <b>165</b> |
| <b>Neurofibromatosis (NF)</b> .....                                | <b>166</b> |
| <b>Neurogenic Bladder</b> .....                                    | <b>168</b> |
| <b>Noise and Environmentally Induced Hearing Loss</b> .....        | <b>106</b> |

## **O**

|                             |            |
|-----------------------------|------------|
| <b>Organ Donation</b> ..... | <b>64</b>  |
| <b>Otitis Media</b> .....   | <b>107</b> |

|                                                 |            |
|-------------------------------------------------|------------|
| <b>Outcomes Measurement.....</b>                | <b>99</b>  |
| <b>Overlapping Chronic Pain Disorders .....</b> | <b>169</b> |

## **P**

|                                              |               |
|----------------------------------------------|---------------|
| <b>Pain .....</b>                            | <b>171</b>    |
| <b>Palliative Care.....</b>                  | <b>172</b>    |
| <b>Pancreatic cancer .....</b>               | <b>20</b>     |
| <b>Pediatric Kidney Disease .....</b>        | <b>43</b>     |
| <b>Pediatric Research Acceleration .....</b> | <b>79</b>     |
| <b>Plasticity .....</b>                      | <b>108</b>    |
| <b>Polycystic Kidney Disease (PKD).....</b>  | <b>44</b>     |
| <b>Presbycusis .....</b>                     | <b>109</b>    |
| <b>Preterm Birth and Stillbirth .....</b>    | <b>80</b>     |
| <b>Psoriasis .....</b>                       | <b>173</b>    |
| <b>Psychosocial Stress in Children .....</b> | <b>81</b>     |
| <b>Public Access .....</b>                   | <b>143</b>    |
| <b>Pulmonary Hypertension .....</b>          | <b>29,124</b> |

## **R**

|                                                                |            |
|----------------------------------------------------------------|------------|
| <b>Relapse Prevention.....</b>                                 | <b>124</b> |
| <b>Research Centers in Minority Institutions (RCMI) .....</b>  | <b>135</b> |
| <b>Royal Centers for Translational Research on Aging .....</b> | <b>95</b>  |

## **S**

|                                                                          |                |
|--------------------------------------------------------------------------|----------------|
| <b>Sarcoidosis.....</b>                                                  | <b>29</b>      |
| <b>Scleroderma .....</b>                                                 | <b>100</b>     |
| <b>Sex Differences .....</b>                                             | <b>176</b>     |
| <b>Sister Study and Breast Cancer .....</b>                              | <b>89</b>      |
| <b>Sleep Disorders .....</b>                                             | <b>30</b>      |
| <b>Social Media .....</b>                                                | <b>21</b>      |
| <b>Social Network Analysis .....</b>                                     | <b>31</b>      |
| <b>Spinal Cord [Brachial Plexus] and Peripheral Nerve Injuries .....</b> | <b>50</b>      |
| <b>Spinal Muscular Atrophy (SMA).....</b>                                | <b>52</b>      |
| <b>Spinal Muscular Atrophy Carrier Screening .....</b>                   | <b>177</b>     |
| <b>Stroke .....</b>                                                      | <b>53</b>      |
| <b>Stroke in Women .....</b>                                             | <b>54, 178</b> |
| <b>Stroke Rehabilitation .....</b>                                       | <b>56</b>      |
| <b>Sudden Cardiac Arrest .....</b>                                       | <b>31</b>      |

## **T**

|                                          |            |
|------------------------------------------|------------|
| <b>Teens and Drug Abuse.....</b>         | <b>126</b> |
| <b>Temporomandibular Disorders .....</b> | <b>35</b>  |

|                                                               |            |
|---------------------------------------------------------------|------------|
| <b><i>Temporomandibular Joint Disorders (TMJDs)</i></b> ..... | <b>101</b> |
| <b><i>Tinnitus</i></b> .....                                  | <b>110</b> |
| <b><i>Tobacco Addiction</i></b> .....                         | <b>127</b> |
| <b><i>Tuberculosis (TB)</i></b> .....                         | <b>65</b>  |
| <b><i>Tuberous Sclerosis Complex (TSC)</i></b> .....          | <b>179</b> |

## ***U***

|                                           |            |
|-------------------------------------------|------------|
| <b><i>Universal Flu Vaccine</i></b> ..... | <b>66</b>  |
| <b><i>Urban-based Network</i></b> .....   | <b>136</b> |

## ***V***

|                                                          |                |
|----------------------------------------------------------|----------------|
| <b><i>Vaccine Development for Hepatitis C</i></b> .....  | <b>67</b>      |
| <b><i>Vestibular Research</i></b> .....                  | <b>111</b>     |
| <b><i>Vitamin D and Chronic Kidney Disease</i></b> ..... | <b>46</b>      |
| <b><i>Vulvodynia</i></b> .....                           | <b>82, 180</b> |

## ***W***

|                                                        |           |
|--------------------------------------------------------|-----------|
| <b><i>Women's Health and the Environment</i></b> ..... | <b>90</b> |
|--------------------------------------------------------|-----------|

## National Cancer Institute (NCI)

### Senate Significant Items

#### Item

**Adolescents** - NCI is encouraged to give additional consideration to adolescents, whose overall risk of contracting most cancers is lower than for adults, but who, because of factors peculiar to adolescence, are less likely to participate in clinical trials and often diagnosed at later stages. In particular, a research focus on health communication strategies for adolescents, their families and their health providers is encouraged. (p. 96)

#### Action taken or to be taken

In 2010, NCI funded five administrative supplements to research grants that are relevant to public awareness of cancers in children, adolescents, and young adults. The purpose of the administrative supplements is to expand and widely implement activities that provide the following:

- 1) Information about ongoing treatment protocols to ensure early access to the best available therapies and clinical trials for childhood/pediatric cancers;
- 2) Information about the late effects of childhood/pediatric cancer treatment to ensure access to necessary long-term medical and psychological care; and
- 3) Information about support services related to childhood/pediatric cancers and those affected by them, such as educational outreach programs for parents, peer-to-peer and parent-to-parent support networks, and resource directories or referral services for financial assistance and psychological counseling.

NCI continues implementation of recommendations made by the 2006 adolescent, young adult oncology progress review group's (AYAO PRG). This progress review group, a public-private partnership between NCI and the Lance Armstrong Foundation's LIVESTRONG Young Adult Alliance (LSYAA), was convened to identify priorities for improving the outcome AYA patients. These activities were grouped under five recommendations:

- Identify characteristics that distinguish the unique cancer burden in the AYAO patient,
- Provide education, training, and communication to improve awareness, prevention, access, and quality cancer care for AYAs,
- Create tools to study the AYA cancer problem,
- Strengthen and promote advocacy and support of the AYA cancer patient, and
- Ensure excellence in service delivery across the cancer control continuum (i.e., prevention, screening, diagnosis, treatment, survivorship, and end of life).

Specific activities and updates on them can be accessed at  
<http://www.cancer.gov/cancertopics/aya>  
<http://www.cancer.gov/cancertopics/aya>

#### Item

**Behavioral Research on Tobacco Control** - The Committee notes that NCI's research on smoking cessation, smokeless tobacco and collaborations with NIDA, NICHD and NHLBI are critical to building knowledge to reduce the use of tobacco by adolescents. The Committee also believes that behavioral science should facilitate FDA regulation of tobacco, including consumer perceptions, development of warning labels, product development and response, risk communication, and cultural effects, and recommends that the NCI support such research. (p.96)

#### Action taken or to be taken

Tobacco use remains the country's leading cause of premature, preventable death—including an estimated one-third of all cancer deaths. NCI-funded research has demonstrated that several factors influence initiation and cessation of tobacco use, including flavorings. Data show that flavored cigarettes are more likely to appeal to youth than those without flavorings. Additionally, the FDA's Tobacco Products Scientific Advisory Committee relies on publications resulting from NCI research as it reports on menthol cigarettes and public health. NCI co-sponsored the "2nd Conference on Menthol Cigarettes," highlighting the science base and research gaps.

NCI research has shown that machine-measured tar and nicotine yields do not provide meaningful information on the amount of tar and nicotine that smokers receive from a cigarette. Smokers of "light" cigarettes are at the same risk for disease as smokers of full-flavor cigarettes. These findings were reported in NCI Tobacco Control Monograph 13, *Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*, which reported that many smokers of "light" cigarettes assume that these products present less of a health risk than other cigarettes, making continued research critical to the implementation of the FDA legislation.

NCI held a workshop, "Cigarette Warning Labels, Packaging & Product Labeling" in 2009 and has since funded a number of ongoing research grants to evaluate the impact and effectiveness of warning labels and packaging in deterring initiation of tobacco use and encouraging quit attempts. The Federal Trade Commission (FTC) used findings reported in NCI Tobacco Control Monograph 9, *Cigars: Health Effects and Trends*, for its recommendation that Congress mandate health warning labels on cigar packages.

In FY 2010, NCI partnered with FDA to fund eight administrative supplements to NCI-funded research to ensure the expansion of knowledge that can be useful for FDA efforts to design and implement tobacco product standards, regulations, and criteria for product-related review. NCI partnered with NHLBI to co-fund research on smoking cessation in hospitalized patients. NCI recently funded two special initiatives to jump-start research in two important areas: improving effectiveness of smoking cessation interventions among low-income adults, and preventing and reducing smokeless tobacco use. In 2011, NCI plans to fund an initiative targeting state and community

tobacco control and media research to address high-priority, population-level research gaps in the areas of secondhand smoke, tax and pricing, and mass media interventions.

NCI-funded research has contributed to the strong evidence base regarding effective treatments and interventions for tobacco dependence. Beginning in 2011, the Federal Employee Health Benefit Program must offer smoking cessation programs and medications without copayments or coinsurance to its beneficiaries. Research is also informing the Centers for Medicare & Medicaid Services as it develops policies regarding smoking cessation as a covered benefit among recipients.

In the largest trial of its kind to date, NCI-funded researchers from the Fred Hutchinson Cancer Research Center found that telephone counseling using motivational interviewing and cognitive behavioral approaches significantly improved 6-month cessation rates in older teens. Given that 20 percent of American high school seniors smoke cigarettes, and that few strategies have been effective at promoting cessation among teen smokers, this finding is very significant.

In an NCI-funded comparative effectiveness study testing five different smoking-cessation aids, researchers found that a combination of the nicotine patch plus the nicotine lozenge was most effective at increasing smoking abstinence. The practice-changing results were published in the *Archives of General Psychiatry*.

#### Item

**Bone defects** - The Committee urges research on how to repair bone defects caused by cancer cells, mechanisms by which cancer cells affect the bone's endogenous cells, the biology of tumor dormancy and the role of tumor stroma in conferring therapeutic resistance. (p. 96)

#### Action taken or to be taken

Bone metastasis is common in prostate, breast, lung, kidney, and thyroid cancers as well as multiple myeloma. The NCI supports basic, translational and clinical research programs directed at bone cancers and recognizes the importance of encouraging research in this area. NCI also supports research in pediatric cancers with bone metastasis such as neuroblastoma and osteosarcoma.

Examples of recent advances made by NCI intramural and NCI-supported extramural investigators include the following:

- Identification of  $\beta 2$  microglobulin, a protein that specifically stimulates bone metastasis and initiation of clinical trials in human multiple myeloma patients to target this protein;
- Characterization of mechanisms by which prostate cancer progenitor cells home to bone, which could lead to the development of new therapies;

- Development of a new method to assess in real-time metastatic progression in the tumor microenvironment, a finding that has provided new insights in to the importance of stromal components of the microenvironment;
- Discovering that insulin like growth factor II (IGFII) occurs in high concentrations in advanced prostate cancer patients and promotes the growth of the cancer in human bone, which suggests that targeting IGFII may be a therapeutic strategy;
- Demonstrating that specific pools of bone cells display different capacities to initiate new sites of bone formation. Another area of high clinical relevance is the role of the tumor microenvironment in promoting tumor growth and bone metastasis.

NCI currently funds several research grants to isolate and characterize dormant tumor cells which are disseminated in the bone marrow. Tumor dormancy is a major area of research emphasis in the recently released Request for Applications (RFA) grant announcement on the Tumor Microenvironment Network (TMEN). The overall goal is to understand the clinical relevance of disseminated tumor cells (DTCs). Metastases can arise from DTCs, which may remain dormant for up to two decades. Importantly, DTCs from early stage prostate cancer patients have a low number of chromosomal aberrations while many more chromosomal aberrations accumulate in DTCs of late stage patients, with heterogeneity observed between DTCs in the same patient. Overall, about 50 percent of patients have dormant cells in bone marrow 10 years after treatment. Understanding the mechanisms by which DTCs are activated might be exploited to reverse actively growing tumors into dormant tumors.

Therapeutic resistance mediated by tumor stroma is another area of research focus in the (TMEN) RFA, which is focused exclusively on understanding the role of the tumor microenvironment in cancer initiation, progression, metastasis, and therapeutic response. Several recent studies indicate that robust stromal infiltration occurs into tumors after chemo- or radiotherapies and may contribute to drug resistance. Even more recently, investigators have identified a stroma-related gene signature that predicts resistance to neo-adjuvant chemotherapy in human breast cancer. In multiple myeloma, tumor associated macrophages have been found to fuse with tumor cells, forming bone-resorbing giant cells that are drug-resistant. Tumor stroma is critical for bone metastasis and plays a key role in conferring therapeutic resistance. Understanding molecular mechanisms of stroma-induced therapeutic resistance can lead to novel anti-stromal agents and new ways to overcome resistance to chemo- and radiotherapy.

#### Item

**Breast Cancer Surveillance** - The Committee commends the NCI's commitment to breast cancer research and evaluation through the support and funding of the Breast Cancer Surveillance Consortium. This research program is critical for improving breast cancer surveillance and improving clinical and community practices. The NCI is urged to

maintain support for this program in order to further the advancement of lifesaving breast cancer prevention research, improve quality of care, and save lives. The Committee also urges the NCI to expand current data collection and surveillance systems to monitor utilization and quality of other widely prescribed cancer screening tools. (p. 96,97)

#### Action taken or to be taken

The Breast Cancer Surveillance Consortium (BCSC) research resources have led to advances in our understanding of breast density and breast cancer risk, identified factors affecting variation in mammography interpretations by radiologists, and enabled research by other investigators. The BCSC leaders have been productive as investigators and collaborators, and their research has improved breast cancer screening practices in the United States. Because of the high regard for BCSC research efforts and accomplishments, NCI has set an extensive plan in motion to support them as they go through the transition to new funding opportunities.

The issues of the comparative effectiveness of screen-film mammography compared to digital mammography, MRI as a diagnostic tool, MRI as a screening tool in high-risk women, the biology of breast density, and biologic determinants of risk all demand that we mount new studies. As a result we have encouraged the investigators to pursue new options and we have created new options for them to pursue. BCSC has submitted an application that addresses the issues of risk-stratified screening and whether individual risk can be used to modify screening intervals; it will be peer-reviewed in February 2011.

NCI will soon release a Funding Opportunity Announcement (FOA) for a new initiative to create screening surveillance networks for breast, colon, and cervical cancer. The FOA for *Population-based Research Optimizing Screening through Personalized Regimens* (PROSPR) should be published in the NIH Guide in fall 2010, and will have a February 2011 submission date. PROSPR's overall scientific goal is to develop multi-site, coordinated, transdisciplinary research to document the entire screening process to evaluate and improve it. The objectives are to: study the comparative effectiveness of existing and emerging screening processes in community practice; study the balance of benefits and harms across recognized cancer risk profiles; conduct preliminary studies to inform future research to optimize screening processes and outcomes; and actively share data and findings with potential collaborators through publications, web portals, and interactions with a consulting panel in order to foster related research. PROSPR will address limitations in our knowledge of screening for cervical, breast, and colorectal cancers. To optimize the screening process, the following additional information is needed: patient risk profiles using existing risk information (i.e., who is at highest risk and who is at lowest risk for developing cancer); screening tests that provide the most cost-effective cancer detection; tests that reach the widest population; the consequences of screening in terms of false-positive tests, resource use, and serious side effects; and the behavioral and health care organizational factors that affect the screening process. This mechanism offers the BCSC an opportunity to submit

applications that propose how best to examine and improve the delivery of screening tests across the networks of providers.

NCI provided \$1 million to BCSC through December 2010, which was five months past the end date of the previous award. As we move into FY 2011, NCI will consider a request for an additional installment of interim funding. Additionally, NCI is creating a contract mechanism to support the development of the BCSC database for wider access and use. The contract will support the statistical coordinating center and maintenance of the aggregated data for use by other investigators.

#### Item

***Clinical Trials Network-*** The Committee is concerned by the findings of the recent Institute of Medicine [IOM] report regarding the NCI clinical trials network. The IOM concluded that the network is too bureaucratic, underfunded, and poorly coordinated. The Committee understands that the NCI requested the report and plans to consider seriously its recommendations. The Committee requests an update on the NCI's progress in implementing the recommendations in the fiscal year 2012 congressional budget justification. (p. 97)

#### Action taken or to be taken

NCI, as a major sponsor of the Institute of Medicine's (IOM) effort to evaluate its Cooperative Group Clinical Trials Program, actively supports the IOM recommendations.

To reduce redundancies and improve efficiency, NCI is consolidating the biostatistical efforts of three of the 10 groups. Peer review will play a central role in facilitating further re-organization, and a new peer review process to evaluate the scientific efforts of the groups is under active development.

To enhance the efficiency of clinical investigation and to improve clinical trial accrual, NCI is distributing standardized clinical trials data management software to all the Cooperative Groups. This is a major effort to harmonize data entry for all NCI-sponsored multisite clinical trials for the first time, on a national basis.

To speed up the clinical trials activation process, NCI has implemented a real-time internet-based dashboard that provides all parties involved in the clinical trials process (investigators, Cooperative Group Administrators, NCI staff) information on where documents reside, the stage of development for the study, and whether the process is meeting its pre-defined deadlines

To reduce bureaucracy and harmonize government oversight and regulation of cancer clinical trials, NCI has established a new collaboration with the FDA's Office of Oncology Drugs. FDA scientists and clinicians will now participate with NCI staff and extramural experts in the NCI's disease-specific scientific steering committees, which will also benefit Cooperative Group trials that may be aimed at obtaining new FDA-approved indications.

To further facilitate collaboration, the NCI has developed and published standardized language for clinical trials agreements and is developing new language to address intellectual property issues involved in biomarker development in its clinical trials.

To improve funding, NCI has increased per case reimbursement rates from \$2,000 to \$5,000 for Cooperative Group phase II studies, and additional funding beyond the standard \$2,000 is being provided for select phase III trials based on their complexity. The increased funding for larger phase II trials is being funded by decreasing the number of smaller, less valuable phase II studies, and by shifting funds previously used to support a larger number of more complex phase III trials at a very low rate.

Finally, as called for in the IOM Report, NCI is developing a credentials registry for investigators and sites to increase incentives for the participation of patients and physicians in clinical trials.

#### Item

**Gastric cancer** - The Committee remains concerned about the rise in deadly gastrointestinal cancers in young people, as highlighted in a recently published study by NCI scientists. The Committee strongly supports the NCI's efforts to address gastric cancer and is pleased to see the inclusion of gastric cancer in the Cancer Genome Atlas. The Committee recommends that NCI convene a workshop of experts in the field of gastric cancer to stimulate research and quickly analyze forthcoming data on this lethal cancer. (p. 97)

#### Action taken or to be taken

NCI shares the Committee's concern about the recent data showing a rise in gastric cancers in young whites detected in NCI's targeted cancer surveillance program for 1977-2006. The Cancer Genome Atlas (TCGA) is in the process of identifying, collecting, and assessing the quality of gastric cancer biospecimens for inclusion into TCGA's genotyping and molecular characterization pipeline. NCI has convened a group of extramural gastric cancer experts to serve on the Gastric Cancer Tumor Project Working Groups. These groups will direct the planning, execution, and analysis of the gastric cancer as part of TCGA. Because the standard of care in treating diffuse gastric cancer (the type that seems to be rising in young people) includes pre-operative treatment, it is difficult to obtain biospecimens from diffuse gastric cancer patients that qualify for inclusion into TCGA, which requires treatment-naïve biospecimens. This requirement is because the drugs given for treatment could affect the biospecimens in ways that could potentially skew research results. In addition, the types of analysis done on biospecimens as part of TCGA require a certain density of tumor nuclei to work. Diffuse gastric cancer biospecimens do not typically have adequate density in the tumor nuclei for analysis as part of TCGA. Therefore, NCI has convened a separate group of gastric cancer experts to focus specifically on scientific opportunities in diffuse type gastric cancer outside of the TCGA framework. Both the TCGA and non-TCGA expert groups include gastric cancer patient advocates. As the TCGA gastric cancer data become available, both groups of experts will be engaged in discussions about

data analysis and future directions of gastric cancer research. We anticipate that the TCGA gastric cancer data will stimulate new areas of scientific exploration and a significant expansion of research opportunities for gastric cancer.

An NCI Genome-Wide Association Study (GWAS) on gastric adenocarcinoma and esophageal squamous cell carcinoma has already revealed a common cancer susceptibility region at *PLCE1*. NCI is following up this finding with mechanistic studies on the effect of the gene variations in this location. A second GWAS will be conducted in a mostly Caucasian cohort to provide further clues about susceptibility regions and whether they differ between populations that experience different rates of gastric cancer. In addition, several studies are being conducted by NCI investigators to evaluate the potential screening biomarkers for gastric cancer.

#### Item

**Liver cancer** - The Committee encourages a stronger focus on liver cancer and urges the funding of a series of Specialized Programs of Research Excellence [SPOREs] focused on this cancer. While SPOREs currently exist for other major cancers, none are focused on liver cancer. (p.97)

#### Action taken or to be taken

NCI's Gastrointestinal (GI) Steering Committee has formed a Hepatobiliary Cancer Task Force, a multidisciplinary task force of liver cancer experts that collaborate to develop new strategies for treatment of hepatocellular carcinoma (HCC), to advance innovative trial designs, and to monitor the progress of ongoing trials. This group has identified key research questions and has generated consensus recommendations for liver cancer research that were published in September 2010 in the *Journal of Clinical Oncology*.

NCI's Gastrointestinal (GI) Specialized Program of Research Excellence (SPORE) at the University of Kentucky's Markey Cancer Center includes a liver cancer project examining the interaction of HCV proteins with important regulators of cell proliferation and the role of such interactions in liver cancer caused by hepatitis C virus (HCV) infection. In addition, NCI is considering one liver cancer SPORE application for possible 2011 funding, with two additional applications expected. NCI will conduct a rigorous scientific review with full and fair consideration of scientific opportunities in this area.

Other NCI-supported research related to HCC include the development of a hepatitis B virus (HBV) transgenic mouse model, which is providing new insights into the disease pathologies that lead to HCC, and the identification of the cellular receptor for HCV infection of liver cells. While HCV, HBV, and excessive alcohol consumption are well-established risk factors for HCC, other factors are emerging, and NCI's epidemiology program is investigating the effects of diabetes, obesity, and other exposures to help explain the increase in incidence rates. NCI's Early Detection Research Network (EDRN) continues to evaluate the use of different biomarkers for the detection of liver cancer, and is currently exploring early biomarkers in urine that may

one day be used as a simple screening test. They are also examining data and biospecimens from population-based studies to determine the putative role of diabetes, metabolic disorders, and obesity in liver cancer risk, as well as continuing to examine the SEER Program – Medicare databases to identify and understand the basis for increasing rates of liver cancer.

Liver cancer will be included in The Cancer Genome Atlas (TCGA), a large-scale effort to compile a comprehensive detailed catalogue of the genetic changes that result in cancer. It is anticipated that data from TCGA will expand our understanding of liver cancer and point to critical new research areas. NCI investigators already identified genetic factors that may play a role in liver cancer development and response to treatment. Researchers have also made progress in the isolation and identification of pathways thought to give rise to new tumors, which may enable the development of targeted therapies.

Finally, the work of NCI's Division of Cancer Prevention illustrates how NCI is leveraging its resources and structure to advance liver cancer research. Through a specialized Gastrointestinal and Other Cancers Research Group (GOCRG), NCI is working with the Small Business Innovation Research program and intramural scientists to develop a vaccine to treat HCV that could offer new possibilities for HCC prevention. Other GOCRG research includes an ancillary study follow-up of a phase III chemoprevention trial in China using green tea polyphenols for individuals at high risk of liver cancer.

#### Item

**Lung cancer** - The Committee continues to urge the NCI to support increased research for lung cancer diagnosis and treatment. (p. 97)

#### Action taken or to be taken

Recent NCI-supported advances in the field of lung cancer diagnosis and treatment cover the full spectrum of the disease from identifying patients with certain genetic mutations that increase the risk for cancer, to the discovery of the role certain immune cells play in the metastatic process. NCI-supported research identified novel lung tumor biomarkers, putative drug targets, and drug effectiveness markers including estrogen, a collection of growth factor receptors, and tumor cell secreted factors. Other advances include characterization of unique gene and microRNA expression profiles to facilitate appropriate cancer diagnosis and patient treatment. New assays for better understanding the biology of lung cancer as well as for screening potential therapeutics were reported. NCI-supported investigators found that cisplatin treatment, a widely used cancer therapy, initially kills non-small cell lung tumors but that chronic treatment can actually promote tumor progression. Other findings have demonstrated that a class of drugs with cancer preventive effects can independently activate a tumor suppressor to block tumor growth and act as a novel cancer treatment.

NCI has a broad lung cancer clinical trials portfolio spanning all three trial phases to test novel targeted therapies alone or in combination with standard treatments, as well as to

conduct translational research studies to advance molecular target characterization, biomarker development, and integration of molecular imaging. One new study will evaluate small cell lung cancer and non-small cell lung cancer patient tumors for a variety of mutations and treatment will be assigned with an agent specific for the mutation identified in each tumor.

NCI provides funding for clinical and translational research in lung cancer diagnosis and treatment through a range of grant mechanisms. Projects include the identification of prognostic and drug effectiveness biomarkers, patient gene and proteomic expression profiling, and assays for detecting circulating tumor cells and tumor-associated antibodies. NCI continues to accept applications for Specialized Programs of Research Excellence (SPORE) grants to improve lung cancer diagnosis and treatment. There are eight active SPORE grants and three pending applications for new SPORES. NCI recently funded a grant to establish a Lung Cancer Mutation Consortium, involving the lung cancer SPOREs and additional collaborators, to collect clinical, pathologic, and genomic data on advanced lung cancer patients to validate or change classifications and to determine eligibility for therapeutic trials directed at the patient's tumor-specific mutation.

#### Item

**Melanoma** - The Committee continues to encourage NCI to work with advocates, researchers, and industry to fund the areas of research-basic, translational, clinical, and prevention-identified by the strategic research plan and to utilize all available mechanisms. The Committee is aware of recent successes in the therapy of molecularly classified subgroups of melanoma that are the result of translating basic research efforts on the genetic signature of melanomas, and is encouraged by the NCI's recent decision to support inclusion of melanoma in the Cancer Genome Atlas [TCGA]. The Committee urges the NCI to develop new models of alliances between industry, academia and foundations in the field of melanoma research to foster earlier validation of biomarker-driven therapies in the laboratory and clinical trials involving key therapeutic agents, regardless of whether they are within the NCI portfolio. Since initial data suggest that concomitant administration of two or more therapies will be required to cure the majority of melanomas, NCI is urged to participate in efforts to develop rational therapeutic drug combinations, including through the use of novel partnerships. The Committee also encourages the Developmental Therapeutics Program to incorporate a more relevant panel of melanoma cell lines based on molecular subtypes, many of which have been developed with NCI funding, to facilitate its goal of identifying novel chemical leads and biologic mechanisms relevant to the prevention and treatment of melanoma. Lastly, the Committee encourages the NCI to explore the feasibility of a screening program, with a focus on high-risk individuals. The Committee requests an update on these requests in the fiscal year 2012 congressional budget justification. (p.97, 98)

#### Action taken or to be taken

NCI recognizes the need to accelerate basic, clinical, and translational research in melanoma. The institute recently strengthened its ability to forge partnerships with

industry and academia by creating a standardized intellectual property (IP) agreement that allows sharing of IP when drug combinations are co-developed. NCI has a broad portfolio of early and later stage clinical trials for melanoma. Targeted therapies alone or in combination are being pursued.

Therapeutics research is examining the microenvironment of melanoma cells and of the multiple targets that sustain or inhibit its growth. Examples of targets being researched by NCI-sponsored investigators include:

- B-Raf—About 50 percent of patients with melanoma have a mutation in this important signaling molecule. A B-Raf inhibitor has recently demonstrated encouraging results.
- cKit—This molecule is mutated in around 30 percent of patients with this skin cancer. Dasatinib is being studied to target this mutation.
- Additional studies are being developed for the therapeutic use of other agents such as those targeting: the Ras protein, which is abnormal in 25-percent of melanomas; vascular endothelial growth factor (using aflibercept, a fusion protein); and a mutation in the ERBB4 molecule (using lapatinib, a drug already used to treat breast cancer).

To create more possible therapeutic targets based on genomic and proteomic changes, NCI expanded The Cancer Genome Atlas to include melanoma cases with associated clinical data.

NCI is also exploring a variety of potential immune-based therapies. One agent, ipilimumab, can improve the survival of patients with advanced melanoma. For early stage melanoma, a phase III study is comparing ipilimumab against interferon. Recently, a Cancer Immunotherapy Trials Network was funded to accelerate clinical trials of other promising cancer immunotherapies. In a phase II trial conducted by the NCI intramural program, the combination of chemotherapy plus or minus radiation with an infusion of immune cells harvested from a melanoma patient's own tumor caused a reduction in tumor burden. A phase I trial is underway with IL-15, which activates tumor-fighting immune cells in melanoma models. Additionally, a protein expressed by normal and tumor melanin-producing cells may be a potential diagnostic for melanoma.

Two chemoprevention trials are evaluating whether lovastatin or sulindac can reverse precancerous changes in unusual moles. In studies using mice, researchers demonstrated that sunscreen use significantly inhibits melanoma formation, which epidemiological data had suggested but not proven. This suggests a possible public health strategy in the future promoting sunscreen use to prevent melanoma. Also in mice, scientists demonstrated that topical application of ingenol-3-angelate, a plant-derived agent, blocked the growth of tumors.

At the basic research level, NCI's Developmental Therapeutics Program has extensively characterized the molecular subtypes for melanoma and other cell lines. An expansion of all cancer cell lines, including melanoma, is currently being considered.

NCI recognizes the importance of screening, particularly in high risk individuals. Scientists at NCI, the University of Pennsylvania, and the University of California, San Francisco have designed an interactive Melanoma Risk Assessment Tool, available on <http://www.cancer.gov>, to help clinicians identify individuals at higher risk of melanoma in order to plan appropriate screening interventions with them. NCI also plans, implements, and maintains a comprehensive program of social and behavioral research to promote the appropriate use of effective cancer screening tests, as well as strategies for informed decision-making, in both community and clinical practice. For example, scientists at the University of Southern California are conducting a randomized intervention study of skin self examination to assess the effectiveness of screening interventions for melanoma.

#### Item

**Nanoparticles** - The Committee encourages the NCI to accelerate the testing and development of nanoparticles for the improved treatment of cancer that are composed of nontoxic materials and remain at the nano-scale in biological fluids, resisting aggregation. (p. 98)

#### Action taken or to be taken

In 2004, NCI established the Alliance for Nanotechnology in Cancer, a multidisciplinary consortium of government and academic research labs with private sector biotech companies at the leading edge of developing and implementing nano-scale diagnostics and treatments for cancer. In parallel, there are also intramural nanotechnology efforts performed at the NCI's Center for Cancer Research (CCR). Over the last five years, Phase I of the Alliance has been effective, leading the way toward over a thousand scientific publications, hundreds of patents, and many clinical trials on new diagnostics and therapeutics.

Achieving clinical evaluation is an important benchmark for work produced by the Alliance. Several different lab tests geared toward detecting tumors that current methods cannot find have entered clinical trials. One such trial uses a microfluidic chamber to simultaneously screen for the levels of hundreds of nucleic acid markers in melanoma patients, before and after treatment, to aid in determining the success of a therapy. Other trials involve improved cancer imaging, investigating several nanoparticles' distinctive magnetic properties coupled with their ability to specifically identify a tumor to improve the resolution of MRI and PET scanners. Other treatment modalities are being clinically tested, including an engineered adenovirus to treat leukemia and nanoparticle encapsulation to deliver sensitive or unstable therapies, such as small-interfering RNA or the potent chemotherapeutic camptothecin, to solid tumors.

The second phase of the Alliance is building on the successes of this collaboration toward clinical deliverables. Phase II is initiating Pathway to Independence Awards in Cancer Nanotechnology Research for new investigators transitioning to the field and creating Cancer Nanotechnology Training Centers to provide multidisciplinary graduate and postdoctoral training. The Alliance is also working with the NCI's Small Business

Innovation Research to better translate the discoveries from research laboratories into clinical development for eventual commercialization. This avenue has already contributed to the founding of over 50 companies.

Central tenets to the development of medical nanoparticles are the potential efficacy of these novel products and their anticipated safety to the patient and environment. Much concern has arisen regarding the capacity of some nanomaterials to form toxic aggregates in solutions and tissues. To address this concern, the NCI has established the Nanotechnology Characterization Laboratory (NCL) to systematically examine nanomaterials produced by academia, government, and industry. Through the NCL's joint management with the National Institute of Standards and Technology and FDA, nanoparticles are examined for their physiochemistry, preclinical toxicology, pharmacology, and efficacy before their approval for Phase I clinical trials. Furthermore, NIEHS is researching the potential environmental effects of nanobiotechnology from their production through their disposal.

Important research continues within the intramural NCI research program, where CCR investigators are exploring the use of RNA as a novel material for the development of biomedical nano-devices. RNA is appealing due to its potential for high structural complexity, diverse functionality, biodegradability, and apparent low toxicity. Scientists have shown computationally designed RNA-based nanocubes can self-assemble and be activated *in vitro*, providing a promising route for biosensor and drug delivery. The CCR investigators have also shown lipid-based nanoparticles may be promising carriers for temporally regulated, targeted drug delivery and may provide a platform for future drug delivery applications.

#### Item

**Neuroblastoma** - The Committee continues to encourage NCI to expand genetic and clinical research on neuroblastoma and convene a state of the science conference on treatment options for high-risk and relapse patients. (p. 98)

#### Action taken or to be taken

Neuroblastoma is a pediatric cancer that is responsible for 7 percent of all cancers in children under 15 years of age and that is the most common non-brain solid tumor in children. Although five-year survival rates have improved for all children with neuroblastoma and now stand at approximately 65 percent, current therapy remains inadequate for approximately one-half of children with the high-risk type of neuroblastoma. NCI-supported clinical trials conducted by the Children's Oncology Group (COG) have defined standard therapy for children with high-risk neuroblastoma, including the positive role of high-dose chemotherapy and of the drug isotretinoin (a derivative of vitamin A that is also used to treat severe acne). Recently a COG clinical trial for high-risk neuroblastoma demonstrated that a new form of immunotherapy using a drug manufactured by NCI (ch14.18) increased the percentage of children alive and free of disease progression. NCI is working with COG researchers and with pharmaceutical companies to obtain FDA licensing for both ch14.18 and for a pediatric formulation of isotretinoin.

The approach that NCI is taking to develop more effective treatments for high-risk neuroblastoma can be divided into four general components: discovery research to identify candidate therapeutic targets, preclinical testing to further validate candidate therapeutic targets and to prioritize specific drugs that modulate these targets, early phase clinical trials to develop evidence for safety and activity of new treatments, and definitive clinical trials to provide convincing evidence for effectiveness for the new treatments. A particular priority in the discovery realm is the identification of genes that are consistently altered in high-risk neuroblastoma as this understanding can provide critical leads for identifying genes and cellular pathways on which researchers should focus in their quest for more effective treatments. The identification of genes that are consistently altered in high-risk neuroblastoma should be largely completed in 2011. Programs such as the Pediatric Preclinical Testing Program, the intramural Pediatric Oncology Branch, the COG Phase 1 Consortium, the New Approaches to Neuroblastoma Therapy (NANT) Consortium, and COG provide pathways for translating discoveries arising from basic and genomics research to the clinical setting.

NCI plans to support several meetings with direct relevance to the development of new treatments for children with high-risk neuroblastoma. A state of the science conference will specifically focus on treatment options and protocols for patients with high risk and relapsed neuroblastoma and will bring together COG researchers and international researchers to develop plans for new treatment strategies to evaluate in clinical trials. Another meeting with direct relevance to high-risk neuroblastoma will focus on new applications of immunotherapy in the pediatric setting, and a third meeting will focus on the genomics of high-risk neuroblastoma.

#### Item

**Pancreatic cancer** - The Committee is disappointed with the lack of progress toward a pancreatic cancer-specific research initiative. The Committee again calls upon the NCI to establish a discrete pancreatic cancer research grant program; re-institute a policy of "exceptions" funding for grant applications whose primary focus is pancreatic cancer; and include more experts in pancreatic cancer on scientific review panels. Further, the Committee notes that the NCI released the "Consensus Report of the National Cancer Institute Clinical Trials Planning Meeting on Pancreas Cancer Treatment" 2 years after the meeting was held and that the report does not include an action plan. The Committee strongly encourages the NCI to develop and implement action steps for research on this disease. (p. 98)

#### Action taken or to be taken

NCI shares the Committee's concern about the poor survival statistics for pancreatic cancer, and has made significant investments into a broad research agenda focused on this disease. A recent analysis of NCI's portfolio showed that NCI pancreatic cancer research funding increased 311 percent between FY2001 and FY2009, while the total NCI budget increased by only 32 percent over the same timeframe. In 2006, NCI established the Gastrointestinal Cancer Steering Committee (GISC) to improve trial design and to prioritize trials in specific GI cancers, and formed seven specific disease-

site task forces to conduct in-depth analyses. The pancreatic cancer task force convenes on a monthly basis to review research concepts and discuss new directions in research. In addition, NCI made it a priority to include pancreatic cancer in The Cancer Genome Atlas (TCGA), which represents an exciting opportunity to obtain comprehensive sequencing, characterization, and analysis of the genomic changes associated with pancreatic cancer. As part of the management of TCGA, NCI is consulting with a variety of pancreatic cancer disease experts, including patient advocates.

In July 2010, NCI convened a group of program and research staff to develop an Action Plan for NCI's future pancreatic cancer research efforts. The group reviewed the current portfolio, discussed the unique challenges of pancreatic cancer in terms of basic biology, diagnosis, and treatment, and evaluated new areas of scientific opportunity. The Action Plan, issued in September 2010, identified future opportunities with the highest likelihood for improving survival rates, including trans-disciplinary workshops focused on topics related to pancreatic cancer, such as diabetes and insulin levels and molecular imaging for detection and diagnosis of pancreatic cancer. Other opportunities include leveraging existing resources such as increasing focus on novel drug discovery and facilitating the development of nanoparticle treatments for pancreatic cancer. Other areas include initiation of a multi-site collaboration for collection of biospecimens, and expansion of large genome-wide association studies on pancreatic cancer to build on the findings of prior pancreatic GWAS (PanScan I and PanScan II), that yielded data that led to the discovery of four novel regions in the genome associated with a risk of pancreatic cancer.

In October 2010, NCI leadership and staff met with pancreatic cancer advocates and discussed the FY2011 Action Plan, explored the opportunities going forward, and identified areas for collaboration, specifically in obtaining pancreatic cancer biospecimens for inclusion into TCGA.

NCI continues to be strongly committed to supporting for high quality research addressing the difficult problem of pancreatic cancer, and NCI's extramural research staff are empowered to propose "exceptions" for promising research proposals which may not otherwise be funded based strictly on the grant review score. NCI leadership has made it a priority to identify and examine novel research ideas, particularly in relation to challenging and complex diseases such as pancreatic cancer.

#### Item

**Social Media** - The Committee encourages the NCI to fund research on how social media can be used to promote health behaviors and social support. (p. 98)

#### Action taken or to be taken

In 2009, NCI's Tobacco Control Research Branch (TCRB) launched the Smokefree Women Web site, (<http://women.smokefree.gov/>), which provides evidence-based information, interactive online resources, quick tips, and assistance specifically tailored to women trying to quit smoking. As part of the outreach strategy to younger women,

the site incorporates social media tools such as Twitter and a companion Facebook page. The Facebook platform acts as a virtual support system, providing a place for women to gather, share, and connect with others trying to quit smoking. Recently, a video blog feature was added to the Facebook page, showing women talking about topics related to smoking. The hope is that these videos will serve as a launching point for discussions on the Smokefree Women Facebook page. Research suggests that social support might have a particular benefit for women who are trying to quit smoking. Participating in conversations and building a community is a way that new media tools, such as Facebook, can help NCI integrate social support into our interventions and remove barriers associated with typical smoking cessation treatments. TCRB also supported research on the use of mobile phone technology provided to DC Tobacco Quitline callers and the expansion of Smokefree.gov (<http://www.smokefree.gov/>), including new links to social media that take advantage of interactive Web technologies to reach new audiences for smoking cessation.

The HCIRB is currently developing a funding opportunity announcement to stimulate exploratory and intervention communication research in the area of social media and health. We have published an overview of social media use in the U.S. and its implications on Health Communication using the Health Information National Trends Survey (HINTS). The analysis points to the potential for social media to narrow the Digital Divide and knowledge disparities, as we found that racial/ethnic minorities, given Internet access, may be more likely to use social media to engage in social networking and information exchange. Using the HINTS data, we also found that cancer survivors, once online, are more likely to use Internet and social media for health-related purposes. Building upon the potential of Web 2.0/social media, the funding opportunity announcement will invite the research community to investigate, using multidisciplinary approaches, ways to promote health behaviors and social support through social/interactive media. We anticipate this program announcement to be reviewed in early-mid 2011 and published by end of 2011.

The NCI Office of Communications and Education engages in user-centered research and formative research that is coupled with findings generated from NCI-funded research and applied to the development of NCI's communication strategies in its public facing social and digital media platforms (Facebook, Twitter, and YouTube).

#### Item

**XMRV (*Chronic Fatigue*)** - The Committee is aware that in October 2009, a group of researchers announced that it had performed blood tests on patients with Chronic Fatigue Syndrome [CFS] and found sufficient evidence of the presence of xenotropic murine leukemia virus related virus [XMRV] to suggest a correlation between XMRV and CFS. While the work has not yet been replicated, the reported research warrants further discussion and investigation. The Committee is aware that NIH will host an international symposium on XMRV in September 2010 to address the pathogenesis and clinical and public health implications of the XMRV virus and to obtain input in developing a coordinated strategy for XMRV research. The Committee also is aware that the second State of the Knowledge Conference is being planned by the Trans-NIH

Working Group on Chronic Fatigue Syndrome for 2011 and is encouraged that this conference will likely make additional recommendations about future funding opportunities for XMRV and CFS research. (p. 121)

#### Action taken or to be taken

Much of the research in CFS, including some current grants on XMRV, is funded through a trans-NIH Program Announcement (PA-08-246 and 247) that was developed through the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome. This Working Group, chaired by the Office of Research on Women's Health (ORWH), has been responsible for most CFS activities over the past 10 years. The Working Group is currently planning a spring 2011 State of the Knowledge Workshop on Chronic Fatigue Syndrome and will issue a new funding opportunity based on the recommendations from this meeting.

Scientists do not know whether there is an association between the presence of XMRV and/or murine leukemia viruses (MLV) and CFS. A number of studies to date have provided conflicting findings; thus, more research is needed to elucidate whether there is a connection between CFS symptoms and evidence of these viruses present in patient blood samples. The NIAID is sponsoring a study to determine whether the presence of XMRV/MLV nucleic acids in the blood is associated with CFS. It is anticipated that this laboratory-based study, utilizing polymerase chain reaction (PCR) screening and other assays, will compare both blood and plasma samples from patients diagnosed with CFS to samples from matched control patients without CFS.

The NHLBI is leading efforts to design and coordinate research studies to evaluate whether XMRV presents a threat to the safety of the supply of blood for transfusion, and is coordinating research to facilitate an independent assessment to guide future work in this area. The NCI contributed to funding the initial report on the discovery of XMRV and its suggested association with prostate cancer, and currently funds several grants on this topic and continues to be involved in discussion and investigation of the XMRV virus and its possible association with disease. The NCI has taken an active role in the development and dissemination of reagents and assays to detect this virus, and co-sponsored an XMRV workshop in September 2010. The objective of the workshop was to assemble an international group of scientists, physicians and epidemiologists to present and discuss, in a public forum, the latest XMRV studies in order to evaluate the state of our knowledge, address controversies, and develop an understanding between experts that will help direct future research. More than 200 researchers from around the world attended the workshop and engaged in a robust discussion about how to gather basic information about the virus and advance the science.

The NIH continues to encourage, and expects to continue to fund, high quality, peer-reviewed applications to elucidate and clarify the role of XMRV and related viruses in human disease.

## National Heart, Lung, and Blood Institute (NHLBI)

### Senate Significant Items

#### Item

**Angiogenesis-** The Committee supports the ongoing research on angiogenesis to examine the ability to detect and treat diseases at early stages. The Committee strongly encourages the Director to coordinate with all relevant Institutes to study correlation of platelet proteomes to angiogenesis with the goal of developing a health marker. (p. 121)

#### Action taken or to be taken

The NHLBI supports a growing portfolio of related research to elucidate the process and underlying mechanism of angiogenesis and to develop treatment strategies for patients with ischemic heart disease and peripheral vascular disease. For example, studies by NHLBI-supported investigators and others have demonstrated that platelets contain both pro-angiogenic and anti-angiogenic factors. Despite increased knowledge of the connection between platelets and angiogenesis, however, the role that platelets play in regulating the growth of new blood vessels from pre-existing vessels is not well understood. Platelet proteomics seeks to identify the structure and function of each platelet protein particle and the complexities of protein–protein interactions. Although still at an early stage, platelet proteomics offers the hope of identifying biomarkers for diagnostics and therapeutics for many disorders that have trans-NIH relevance. Several laboratories are currently applying platelet proteomics to better understand the many angiogenic factors that are stored in platelets and released after platelet activation. This knowledge will be critical for identifying markers of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic interventions. Over 1,100 platelet proteins have been identified using proteomic techniques, and proteomic data about platelets have become increasingly available in integrated databases. This “virtual platelet” knowledge base could further accelerate the understanding of platelets in the processes of angiogenesis and various diseases.

#### Item

**Aortic Aneurysm and Dissection -** The Committee commends the NHLBI for its strong support of the Genetically Triggered Thoracic Aortic Aneurysms and Other Cardiovascular Conditions Registry (GenTac). (p. 98)

#### Action taken or to be taken

Although thoracic aortic aneurysms (TAAs) generally occur in older persons as a consequence of hypertension or atherosclerosis, their appearance in young adults is more typically associated with rare genetic disorders such as Marfan syndrome. The NHLBI-supported Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions Registry (GenTAC) serves as a resource to advance treatment of patients with genetically induced TAAs. The original program, awarded in September 2006 with 5 recruiting sites and a data coordinating center, quickly established feasibility of the registry infrastructure. Its renewal, awarded in September 2010, will enrich datasets by

collecting longitudinal follow-up data, improve data quality by the addition of imaging and phenotyping capabilities, promote access and use of the registry, and enable limited new enrollment to enrich the cohort with subgroups of high scientific interest via the addition of two recruiting sites. To date over 2,200 patients have been enrolled.

Information about GenTAC is disseminated to potential study subjects using a number of avenues. Most notably are collaborations with patient advocacy groups such as the National Marfan Foundation, the Ehlers-Danlos National Foundation, and the Turner Syndrome Society. These organizations have well-established resources for providing information to patients such as Web sites, newsletters, and national conferences. A recruitment brochure has been developed that explains the goals and basic procedures of the study. Finally, the study Web site, <http://gentac.rti.org> also informs potential subjects about the registry.

#### Item

***Congenital Heart Disease*** - The Committee commends the NHLBI for the development and implementation of the Bench to Bassinet program in an effort to provide multidisciplinary translational research for congenital heart defects across the lifespan. The Committee urges the NHLBI to continue its work with patient advocacy organizations, other NIH Institutes, and the CDC to expand collaborative research initiatives and other related activities targeted to the diverse life-long needs of congenital heart defect survivors. (p. 98)

#### Action taken or to be taken

The NHLBI Bench-to-Bassinet Program is a collaborative effort bringing together cardiovascular basic, translational, and clinical researchers to accelerate the movement of scientific discoveries to clinical practice. Initiated in September 2009, it began with a one-year planning phase to support program development and implementation. Planning activities included designing a multi-center Congenital Heart Disease GEnetic NEtwork Study (CHD GENES), initiating a biorepository of DNA specimens, and selecting program-wide services to collect and analyze genetic data efficiently. The research phase is now under way, with projects directed toward identifying genetic causes of congenital heart disease, relating genetic defects to lifelong disease outcomes in congenital heart disease survivors, and uncovering the biological basis underlying congenital heart disease.

The NHLBI will continue support for this collaborative program and seek opportunities to work with patient advocacy organizations (e.g., the Children's Heart Foundation, Mended Little Hearts, and the Congenital Heart Information Network), other NIH components, and the CDC to increase the scope of collaborative activities and better address the needs of congenital heart defect survivors. The NHLBI has provided support to the Adult Congenital Heart Association to enable them to partner with the multi-center clinical research group Alliance of Adult Research in Congenital Cardiology for a study of lapses in clinical care experienced by adult survivors of congenital heart disease (HEART-ACHD). The study is in the final stages of data collection and analysis. The NHLBI also has an ongoing collaboration with the National Marfan

Foundation to conduct a clinical trial jointly with the NHLBI Pediatric Heart Network comparing standard therapy using the beta-blocker atenolol with therapy using the angiotensin II receptor-blocker losartan. They will determine which drug is better at slowing the progression of aortic root enlargement in children with Marfan syndrome. The study also compares side effects that can occur when taking either of these drugs. Patients are being followed through 3 years of treatment at over 20 sites in North America and Europe. The NHLBI serves with the CDC, American Academy of Pediatrics, American Heart Association, and other associations as part of the Congenital Heart Public Health Consortium. The mission of the consortium is to enhance and prolong the lives of those with congenital heart disease through surveillance, population-based research, education, health promotion, advocacy, and policy development.

#### Item

***Diamond-Blackfan Anemia (DBA)***- The Committee understands that NHLBI's research initiatives regarding DBA continue to demonstrate the benefits of translational research and have led to important insights into the biology of blood disorders, birth defects, and cancer development and to a breakthrough in one of the first human disorders linked to a ribosomal protein defect. The Committee understands that, prior to this discovery, changes in the ribosomal protein gene expression were considered inconsequential but have now proven to be a fundamental unit of cellular function. The Committee commends the NHLBI for its attention to this important area of disease research and strongly encourages the Institute to continue efforts to make understanding the role of ribosomal proteins in DBA and related marrow failure diseases an investigative priority. (p.98,99)

#### Action taken or to be taken

Remarkable progress has been made since the NHLBI awarded 16 research grants in September 2004 through the initiative "Molecular Mechanisms Underlying Diamond-Blackfan Anemia (DBA) and Other Congenital Bone Marrow Failure Syndromes." The program has yielded a dramatic increase in our understanding of the molecular mechanisms underlying rare bone marrow failure disorders and overwhelming evidence that the ribosome, long thought of as a fundamental housekeeping organelle, can be the target of pathogenic mutations that lead to human disease. More than 11 ribosomal genes implicated in various congenital bone marrow disorders have been discovered, providing the first evidence that a human disorder is linked to a ribosomal protein deficiency or a defect. These findings indicate that decreased expression of ribosomal proteins can have pathogenic consequences within bone marrow and during development of other tissues. Many of the grantees supported by this initiative have successfully competed for follow-on funding to continue their work on DBA and other bone marrow failure disorders.

In 2008 the NHLBI, in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases and the Centers for Disease Control and Prevention, sponsored a workshop on the role of ribosomal biogenesis in disease. The meeting generated recommendations to move ribosome biology from basic research into translational

studies via synergy among clinicians, bone marrow experts, and basic ribosome biologists. The Institute is exploring avenues to foster such synergistic efforts. Moreover, a new program announcement, “Ribosomal Disorders and Their Role in Inherited Bone Marrow Failure Syndromes” is being developed with the goal of extending our understanding of the molecular and cellular mechanisms underlying ribosomal disorders, their preferential effects on hematopoiesis, and their role in bone marrow failure syndromes such as DBA.

#### Item

**Heart Disease** - The Committee strongly urges the NHLBI to aggressively expand and intensify its investment in basic, translational and clinical heart research to capitalize on advances and burgeoning scientific opportunities. The Committee supports the allocation of increased resources for heart research to expand current studies; support promising and novel research; through all available mechanisms, as appropriate; and accelerate implementation of priorities highlighted in its Division of Cardiovascular Diseases Strategic Plan. (p. 99)

#### Action taken or to be taken

The NHLBI continues to invest considerable resources in research to address heart disease, the leading cause of death in the United States and a source of considerable suffering and health-care cost. The Institute’s Strategic Plan identifies exciting and compelling research opportunities in three broad areas of emphasis — basic, translational, and clinical research. Efforts in these areas include the following:

The NHLBI continues to support a broad portfolio of investigator-initiated basic research projects; they are the engine that generates new biomedical discoveries. In addition, the Institute is devoting a portion of its resources to special initiatives in areas that require a concerted multi-disciplinary approach, particularly the development of high-throughput technologies such as genomics, proteomics, and nanotechnology. The funding of genome-wide association studies in many large epidemiologic cohorts illustrates the Institute’s commitment to advancing such cutting-edge research.

Translational research is an area of major emphasis. The NHLBI has developed multidisciplinary programs that are designed to bridge the traditional gap in translating pre-clinical findings to clinical settings and to promote cross-fertilization of basic and clinical research. For example, the Cardiovascular Cell Therapy Research Network fosters a collaboration of basic researchers, interventional cardiologists, imaging specialists, and statisticians to perform early-phase trials in adult stem cell therapy. NHLBI has also established the Cardiac Translational Research Implementation Program (C-TRIP) to support the planning and execution of clinical safety and efficacy trials to translate promising new cardiovascular therapies from the laboratory to patient care.

The NHLBI has long been a supporter of extensive clinical research involving a diversity of patients of all ages. In addition to its traditional leadership in clinical trials designed to test paradigms for the prevention and treatment of cardiovascular diseases, the Institute

has increased its emphasis on comparative effectiveness research to evaluate alternative treatment strategies in “real world” settings. Some examples are comparisons of angioplasty and stenting versus medical management of renal and peripheral arterial disease and comparisons of alternative imaging techniques for diagnosing heart attack in emergency rooms and outpatient settings.

#### Item

**Marfan Syndrome** - The Committee commends the NHLBI for its continued support of research related to Marfan syndrome, particularly in the area of pediatrics. The Committee encourages the Institute to facilitate support of research related to surgical outcomes for adult patients who undergo procedures to repair compromised aortas and valves. (p.99)

#### Action taken or to be taken

The NHLBI continues its support for clinical, translational, and basic research related to Marfan syndrome in children and adults. A clinical trial run by the NHLBI Pediatric Heart Network, a multicenter collaborative clinical research group, is comparing standard therapy using the beta-blocker atenolol with therapy using the angiotensin II receptor-blocker losartan to determine which drug is better at slowing the progression of aortic root enlargement in children with Marfan syndrome. The study also compares side effects that can occur when taking either of these drugs. Patients are being followed through 3 years of treatment at over 20 sites in North America and Europe. The NHLBI has expanded the potential scientific yield of the trial through support of several promising ancillary studies. The National Marfan Foundation generously funds various aspects of the study.

The NHLBI has renewed and expanded its support for the Genetically Triggered Thoracic Aortic Aneurysms Registry (GenTAC), which serves as a resource to advance treatment of patients with genetically induced thoracic aortic aneurysms (TAAs). Although TAAs generally occur in older persons as a consequence of hypertension or atherosclerosis, their appearance in young adults is more typically associated with rare genetic disorders such as Marfan syndrome. GenTAC will collect longitudinal follow-up data, improve data quality by adding imaging and phenotyping capabilities, promote access and use of the registry, and enable limited new enrollment to enrich the cohort with subgroups of high scientific interest via the addition of 2 recruiting sites. To date over 2,200 patients have been enrolled. GenTAC data are available to the broader scientific community for analysis of long-term outcomes of surgical repair. In addition, the NHLBI will continue to support scientifically meritorious investigator-initiated research in promising areas, such as surgical outcomes for adult patients who undergo procedures to repair compromised aortas and valves.

The NHLBI supports a number of investigator-initiated grants conducting basic research on growth factors and proteins known to be involved in Marfan syndrome disease progression. Funds made available by the American Recovery and Reinvestment Act are being used to expand this support to four grants conducting basic research on

proteins involved in valve disease and translational research to seek biomarkers that may predict which patients are at risk of developing TAAs.

Item

***Pulmonary Hypertension (PH)*** - The Committee continues to support research in this area and commends the NHLBI for convening a working group on pulmonary hypertension to identify priority research topics. The Committee urges support for the working group's agenda and encourages the Institute to collaborate with the PH community to raise awareness of the disease among the general public and healthcare providers. (p.99)

Action taken or to be taken

The NHLBI is working with the PH community on several fronts. The recent workshop "Strategic Planning for Lung Vascular Research," spearheaded by key PH investigators and clinicians, identified several priorities for advancing PH research, diagnosis, and treatment. An immediate result has been collaboration with the Pulmonary Hypertension Breakthrough Initiative to generate a new program that will make human PH tissue samples widely available to the PH and vascular research communities. This activity launches a much-needed translational research effort to promote direct investigation of PH in human tissues and cells that may lead to identification of new targets for treating PH.

A second initiative being developed will support innovative research focused on right ventricular disease, the ultimate cause of death in PH patients. The program will bring together multidisciplinary teams in a groundbreaking effort to understand the failing right ventricle and to develop diagnostics and new treatments.

Plans for the future include a workshop to evaluate the status of pulmonary thromboembolism research. Because circulating elements in the blood are now recognized as playing an important role in lung vascular health, new treatments for PH patients may be discovered through better understanding the role of blood elements and clotting in PH disease progression.

NHLBI staff interacts with the Pulmonary Hypertension Association, American Heart Association, and the American Thoracic Society at their annual meetings to provide up-to-date information on Institute activities.

Item

***Sarcoidosis*** - The Committee is concerned that little progress has been made in understanding the cause of sarcoidosis, which can cause chronic debilitating or life threatening heart, neurological and internal organ disease. To date, there are no effective treatments options. The Committee strongly encourages the NHLBI to place a higher priority on sarcoidosis by intensifying its investments in basic research, clinical investigations and trials. (p. 99)

Action taken or to be taken

Sarcoidosis is a disease of longstanding priority and recently intensified focus for NHLBI. A new research effort has been initiated that will support multidisciplinary teams to conduct state-of-the-art genomics, study the lung microbiome, and gather detailed clinical information. The program seeks to define the molecular, cellular, and clinical characteristics of recently diagnosed sarcoidosis patients with the expectation that the resulting data will provide a basis for better disease definition, patient sub-type classifications, and development of new diagnostics or therapies.

The Institute is also supporting an American Recovery and Reinvestment Act (ARRA)-funded project to identify the genetic mutation or mutations that predispose to sarcoidosis. Other projects are investigating the causes of sarcoidosis, genes that may confer susceptibility, and more efficacious ways to administer immunosuppressive therapy. A clinical trial of atorvastatin for treatment of sarcoidosis is being conducted in the NHLBI intramural program.

The NHLBI leads the Trans-NIH Committee on Sarcoidosis to facilitate NIH-wide discussions of research progress and to identify research topics for future collaboration. We continue to be interested in receiving and supporting meritorious research applications in sarcoidosis, and to encourage their submission via various solicitations. For example, a program announcement titled “Sarcoidosis: Research into the Cause of Multi-organ Disease and Clinical Strategies for Therapy” solicited projects on the etiology and management of sarcoidosis.

#### Item

**Sleep Disorders** - The Committee is impressed by research demonstrating a clear association between sleep disruption and cardiovascular disease, diabetes, hypertension, and stroke, as well as workplace and traffic accidents. The Committee encourages increased research and education programs to decrease the impact of sleep problems on health and safety. (p.99)

#### Action taken or to be taken

In a comprehensive effort to reduce the impact of sleep problems on health and safety, the NHLBI is pursuing a strategy that includes fundamental research, clinical trials, translation, education, and the promotion of national sleep health objectives. A number of new NHLBI initiatives are addressing the links between sleep and health and safety through studies of the connection between sleep and abnormalities in heart, lung, and blood tissues; sleep-disordered breathing during pregnancy; and the effects of adolescent sleep deprivation on cardiovascular risk factors and disorders such as obesity. The generalizability and clinical implications of findings from such sleep research will be ascertained through integration with existing large population studies of cardiovascular disease risk.

Clinical trials are being organized to develop the evidence base for medical practice. Examples are an evaluation of surgery (adenotonsillectomy) as a treatment for sleep-disordered breathing in young children, a study to determine whether patient adherence

to physician-prescribed positive airway pressure therapy for sleep apnea improves real-world driving safety, and a pilot study of positive airway pressure therapy to reduce the occurrence of cardiometabolic disease in high-risk adults.

A critical step toward improving sleep-related health and safety is dissemination of research results. A new NHLBI educational research initiative in 2011 will focus specifically on the development of portable and innovative knowledge-transfer strategies to enhance evidence-based practice among health-care providers, facilitate interdisciplinary team science, and improve the health of special populations and communities. “Sleep Health” goals for the nation will be published as part of the anticipated DHHS Healthy People 2020 report.

#### Item

**Social Network Analysis** - The Committee commends the NHLBI for contributing to a recent trans-NIH initiative on social networks. Social network analysis can be used to study the transmission of viral infections, behaviors, attitudes, information, or the diffusion of medical practices within social networks. (p.99)

#### Action taken or to be taken

The purpose of the trans-NIH initiatives on social networks is to encourage basic research that can lead to new applications of social network methods and theory to improve human health. Two funding opportunity announcements were released simultaneously — one soliciting applications for R01s (research project grants) and the other for R21s (exploratory/developmental research project grants). Awards are expected to be made in April 2011. The NIH is committed to this vital area of research and hopes that additional applications will be submitted for the two future receipt dates (May 11, 2011, and May 11, 2012).

#### Item

**Sudden Cardiac Arrest** - The Committee is deeply concerned by the prevalence of and mortality rates associated with SCA and urges the NHLBI to make this condition a top research priority. In particular, the Committee strongly encourages the NHLBI to investigate the use of induced hypothermia therapy as both a life-saving treatment for SCA victims and one that is demonstrating promise in improving neurological outcomes for patients. In addition, the Committee encourages the NHLBI and the NINDS to enhance and coordinate data collection associated with SCA and hypothermia therapy in particular. (p.99,100)

#### Action taken or to be taken

As many as 450,000 people die of SCD each year in the United States. Survivors often experience devastating neurological impairment. This condition is a top priority to the NHLBI where over 70 studies are currently being funded that focus on developing better ways to detect the impending onset of SCA and to prevent it.

NHLBI-supported researchers are also investigating the effectiveness of new strategies, such as therapeutic hypothermia to improve survival and neurological outcomes in

persons with SCA. As such, NHLBI is supporting two large trials using therapeutic hypothermia as a treatment for SCA.

The first is a multicenter study to investigate the effectiveness of body cooling (or therapeutic hypothermia) in infants and children who have had cardiac arrest. Therapeutic hypothermia has been shown to be effective in adults after cardiac arrest and in newborn infants after birth asphyxia, or lack of oxygen, to improve survival and neurological outcomes, but has not been studied in infants or children after cardiac arrest. The Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trial aims to improve survival rates and minimize brain injury in children who experience cardiac arrest.

Additionally, the NHLBI Resuscitation Outcomes Consortium is developing a protocol for clinical trials evaluating the effectiveness of induced hypothermia and other interventions to reduce SCD when cardiac arrest occurs in or outside a hospital setting. Specifically, investigators will be looking at therapeutic hypothermia as a means of cooling the body to reduce multi-organ dysfunction and neurologic injury.

NHLBI is involved in a trans-NIH task force with NINDS, examining sudden unexpected death. NINDS has scientific interest in SCA in the form of Sudden Unexpected Death in Epilepsy (SUDEP). While therapeutic hypothermia has not been discussed as a potential intervention, NHLBI is open to future collaborations with NINDS in this area.

## National Institute of Dental and Craniofacial Research (NIDCR)

### Senate Significant Items

#### Item

**Behavioral Research** - The Committee applauds the NIDCR's recognition of behavior as a critical factor in oral health, and it encourages research on the development of educational and behavioral oral health promotion interventions to improve maternal and infant oral health. (p. 100)

#### Actions taken or to be taken

The NIDCR is committed to the support of basic and applied research in the behavioral and social sciences, as articulated in the 2009-2013 NIDCR Strategic Plan. As evidence of our commitment, we are in the process of re-invigorating the NIDCR behavioral and social sciences intervention research program, based on the recommendations of expert consultants from diverse stakeholders. The importance of maternal and infant oral health is reflected in each of these recommended activities, through the inclusion of expert investigators focusing on maternal and infant oral health, through the highlighting of relevant examples, and through the encouragement of work focused on this important area of oral health research.

Among the recommended activities the NIDCR has implemented already are: the establishment of an intensive training workshop to encourage use of rigorous methods for developing and testing oral health interventions; the development of a Funding Opportunity Announcement to support pilot testing of new interventions to improve oral health; and the sponsorship of a special journal issue focused on providing researchers with expert guidance in conducting cutting-edge, rigorous intervention research in oral health. In addition to large-scale programmatic activities in support of maternal and infant oral health, the NIDCR continues to support investigator-initiated grant projects with a maternal and infant focus. Among these are grants developing and testing a group-based oral health intervention for pregnant women, oral health promotion interventions utilizing lay community members (e.g., promotoras, trained community health workers), and integrating maternal and infant oral health care into non-traditional settings (WIC clinics, Early Head Start programs, school settings, primary care clinics, infectious disease clinics, public housing communities, etc.).

In addition to these intervention studies, the NIDCR supports the key foundational research required before intervention development begins. These projects include those studying the psychosocial needs of infants and families with oral disease or associated conditions, including early childhood caries, craniofacial anomalies (cleft lip and palate, craniosynostosis, hemifacial microsomia), very low birth weight and early respiratory problems, and family dietary patterns and early obesity. The NIDCR also supports research on the social determinants of oral health and disease among infants and their mothers, including studies of childhood oral health in households in which interpersonal

violence exists, or parents have varying degrees of oral health knowledge, or in communities in which there is limited access to quality oral health care.

#### Item

***Craniofacial Skeleton*** - The Committee urges continued support for research on the effects on the craniofacial skeleton of systemic drugs prescribed for the treatment of bone diseases, including factors predisposing individuals to osteonecrosis of the jaw, as well as novel approaches to facilitate bone regeneration. (p. 100)

#### Actions taken or to be taken

NIDCR remains committed to supporting research about bone diseases and bone regeneration. The first goal in our 2009-2013 Strategic Plan includes the following objective: Facilitate reconstruction and regeneration of diseased or damaged oral and craniofacial tissues and organs through biological, bioengineering, and biomaterials research approaches.

Bone diseases afflict many Americans. Thirty-four million Americans suffer from osteopenia, a condition in which bone mineral density is lower than normal. Another eight million women and two million men have the more serious condition of osteoporosis, which is the loss of bone mass. Bone fractures that occur because of osteoporosis are associated with significant illness and economic burden. The NIDCR supports basic bone biology studies that seek to identify the molecular signals and pathways regulating bone formation and bone resorption. Information from these studies will shed light on basic mechanisms as well as therapeutic strategies for combating bone loss.

The craniofacial skeleton can also be harmed by treatments for illness, such as drug treatments for cancer. In particular, reports in the scientific literature suggest an association of high-dose, intravenous forms of bisphosphonate with osteonecrosis of the jaw (ONJ). ONJ has also been observed in people taking oral forms of bisphosphonate for osteoporosis or other diseases. The primary symptom of ONJ is the exposure of diseased bone in the upper or lower jaw because of lesions in the oral tissues. The lesions themselves often but not always develop following invasive dental procedures. ONJ can be complex, painful, and difficult to treat. In 2006, the NIDCR released a series of funding opportunity announcements soliciting research about the pathophysiology of bisphosphonate-associated ONJ, risk factors for its development, and onset and progression of the condition. Through these solicitations, the NIDCR is now supporting several studies on the epidemiology and basic biology of ONJ. The NIDCR is committed to research in this area and has developed plans to reissue the funding opportunity announcements. The goal is to stimulate additional research on the genetic, molecular, and cellular basis of ONJ, novel approaches to augment bone repair, and clinical observational studies on patient susceptibility and treatment options. These studies will complement an ongoing effort by NIDCR's three regional dental practice-based research networks to determine risk factors for developing bisphosphonate-associated ONJ. The knowledge gained by such research will be

applied to the prevention, management, and treatment of individuals with ONJ and other craniofacial skeletal problems.

#### Item

**Temporomandibular Disorders** - The Committee appreciates the Institute's recent support for research on TMJD but notes that prospects for significant progress are hampered by the lack of a coherent body of knowledge on the etiology and pathogenesis of these conditions. Therefore, as it did last year, the Committee requests the NIDCR to take the lead in developing a comprehensive multidisciplinary 5-year TMJD research plan that articulates the strategies and goals necessary to resolve the issues that have plagued the TMJD field over the decades. The plan should include research to develop definitive diagnostic criteria; support an updated epidemiology, including a count of co-morbid conditions; examine genetic and other factors that increase risk for TMJD; and support endocrine, immune and nervous system research on pain mechanisms and treatments. The plan's research goals should incorporate the appropriate mix of multidisciplinary, basic, clinical and translational science, recruitment strategies to recruit scientists from the many pertinent disciplines, and meaningful training programs to enlarge the pool of investigators and indicate what funding mechanisms should be employed. The Committee requests an update on this request in the fiscal year 2012 congressional budget justification. (p. 100)

#### Actions taken or to be taken

TMJDs are a complex set of diseases involving tissues of the face and the temporomandibular joint. TMJDs may occur together with other chronic painful disorders such as fibromyalgia, trigeminal neuralgia, chronic fatigue syndrome, irritable bowel syndrome, vulvodynia, interstitial cystitis, and migraine headache. The NIDCR continues to support endocrine, immune, and nervous system research leading to the discovery of common etiological and pathophysiological mechanisms underlying this set of chronic disorders that overlap with TMJDs. The NIDCR has published its five-year Strategic Plan for 2009-2013. The plan highlights research priorities for basic, clinical, and translational research and training, and provides the framework for the future of TMJD research, including new discoveries through genetic and genomic approaches. In addition, the NIDCR recently outlined a TMJD and Orofacial Pain program that articulates the programmatic, health, and research goals for this research topic for the next six years. This program will expand NIDCR's commitment to orofacial pain and genetics research and position the TMJD research field to take advantage of genomic era translational and clinical research opportunities. The goal of this program is to better prevent, treat, and diagnose TMJDs and other orofacial pain disorders. The top priority research areas include research capacity building; understanding basic and behavioral mechanisms of the etiology and pathology of TMJDs; translational research on mechanisms of disease progression and treatments; and clinical research on prevention and treatment with a focus on preventing or reversing the transition from acute to chronic pain. Advances in genetics will drive new directions in TMJD research. The NIDCR is focused on bringing new scientific expertise, tools and approaches to TMJD research to take advantage of these new genetic findings. Young investigators, junior faculty, and

trainees with expertise in systems and computational biology, biobehavioral science, and neuroplasticity will be recruited to expand the community of researchers engaged in TMJD research. Recently, a “Concept” on developing research capacity in TMJD and pain research was approved by the NIDCR Advisory Council. The NIDCR will use funding mechanisms consistent with the goals and outcomes of the initiatives emerging from this Concept.

NIDCR staff has attended a recent workshop and a conference related to TMJD research. NIDCR sought research recommendations from the organizers of these meetings and these recommendations have been useful in guiding the NIDCR in formulating the research plan for TMJDs. The “International Consensus Workshop: Convergence on an Orofacial Pain Taxonomy” was held in March 2009. Research recommendations from this meeting centered on developing a better research and clinical diagnostic classification for TMJDs including the development of disease ontology; increasing research on risk factors for disease and disease progression; development of better pain assessments; and tailored treatments for TMJDs. The “Second TMJ Bioengineering Conference” was held in November 2009. Research recommendations from this meeting centered on a greater emphasis on in vivo regeneration of TMJ tissues, the need for molecular imaging studies for diagnosis and treatments of TMJDs, the development of biomechanical models that are useful for clinically relevant problems, and additional training for students and postdoctoral fellows.

## National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

### Senate Significant Items

#### Item

***Chronic Kidney Disease (CKD) and Asian/Pacific Islanders-*** The Committee notes that the incidence of CKD among the Asian/Pacific Islander [API] population is higher than for most other groups. The Committee urges the NIDDK to focus research efforts on preventing chronic kidney disease among this population. (p.101)

#### Action taken or to be taken

The NIDDK shares the Committee's concerns regarding the impact of chronic kidney disease (CKD), which disproportionally affects members of several minority populations. In Asian/Pacific Islanders (API), much of the excess burden of chronic kidney disease is due to higher rates of type-2 diabetes, the most common cause of chronic kidney disease. NIDDK's extensive basic and translational research programs that address obesity, diabetes, and CKD among American Indians and Alaska Natives have deepened our understanding of these health disparities. Much of the knowledge gained through these efforts is also relevant to the burden of CKD in API.

NIDDK held a scientific workshop in November 2010 on "Translating CKD Research into Improved Clinical Outcomes" that focused on interventions for the prevention, treatment, and management of chronic kidney disease in individuals and communities at highest risk. A follow-up research solicitation has been published for 2011. The NIDDK encourages applications in response to this solicitation from investigators working with API communities who are interested in issues related to translational research for CKD. Relevant research areas will likely include the science of translational research, health disparities, health literacy, multidisciplinary approaches, and collaboration with federal agencies.

The NIDDK's National Kidney Disease Education Program (NKDEP) focuses its efforts on populations at high risk for CKD and health care providers who serve those populations. The NKDEP has developed versions of its materials and clinical tools for specific populations, for example, African Americans and American Indians, and Chinese and Vietnamese. Additionally, the NKDEP has a pilot project with community health centers to improve CKD detection and care that aims to help the centers adopt changes that will improve the detection and management of CKD, as well as to identify a set of best practices that can be shared with health centers nationwide. Finally, the NIDDK-led Kidney Interagency Coordinating Committee (KICC) exists to share information, identify and disseminate promising practices and tools, and foster cross-agency collaboration. The KICC would be well suited to help organize an interagency effort to address the issue of CKD in the API population.

Item

**Glomerular Disease Research-** The Committee is pleased that the NIDDK and the NCMHD are collaborating on a scientific conference on the *MYH9* gene, which has been linked to the high prevalence of focal segmental glomerulosclerosis among African-Americans, and it urges the NIDDK to collaborate with the NCMHD to support expanded research on this condition through the Nephrotic Syndrome Rare Disease Clinical Research Network. (p. 101)

Action taken or to be taken

In the spring of 2010, the NIDDK convened a scientific meeting on the *MYH9* genetic region. The meeting was attended by staff from the NIDDK and the National Center on Minority Health and Health Disparities (now the National Institute on Minority Health and Health Disparities (NIMHD)), as well as staff from other ICs including the National Human Genome Research Institute; the National Heart, Lung and Blood Institute; and Office of Behavioral and Social Sciences Research. The speakers and attendees included researchers with multidisciplinary viewpoints, including sociologic, genetic, anthropologic, nephrologic, and public health perspectives. This conference reviewed genetic, public health, ethical and social implications of these new findings, and conference participants provided feedback to the NIH regarding potential future research directions. Patient-centered approaches to research regarding transmission and utility of genetic information were highlighted as research opportunities, along with numerous types of preclinical studies to elucidate the biological basis of the observations. In 2010, researchers reported a major finding that variants in the *APOL1* genetic region, which is adjacent to the *MYH9* genetic region, may be responsible for the differential risk of developing kidney disease in African American populations. It is thought that these variants may also provide a degree of protection against African sleeping sickness, a degenerative and potentially fatal condition caused by a parasite that is endemic to Africa. If true, this would explain why these variants are more commonly found in individuals of African descent, despite the increased risk of kidney disease they confer.

The Nephrotic Syndrome Study (NEPTUNE) is supported by the NIH Office of Rare Disease Research (ORDR) and the NIDDK. This consortium of research groups receives significant support from two patient advocacy groups: The NephCure Foundation and the Halpin Foundation. Currently, the consortium is (1) establishing a collaborative, integrated, cost-effective infrastructure to conduct clinical and translational research to perform longitudinal observational cohort studies for 450 participants over 30 months; (2) administering a training program for post-doctoral and junior faculty trainees preparing for clinical and translational research in glomerular diseases; (3) working with the Rare Diseases Clinical Research Network Data Management Coordinating Center and NephCure to develop a Web-based exchange platform for the public, healthcare providers, and scientists; and (4) implementing a number of pilot and ancillary studies. The first pilot study has been initiated and three ancillary projects are under review. In addition, the training program is in place and a request for applications has been released. A patient contact registry has been established and to date more than 670 potential participants have self-registered. Also, the consortium is

collaborating with the NephCure Foundation and the Halpin Foundation on developing several community outreach tools. Already, several patient education brochures have been developed, as well as a video, both of which are excellent outreach tools.

The NIDDK, NIMHD, ORDR, and other NIH Institutes and Centers will continue to build on their collaborations to better understand and address the high prevalence of focal segmental glomerulosclerosis in African Americans.

#### Item

**Inflammatory Bowel Disease (IBD)**- The Committee encourages expanded support for research on IBD as identified in the NIH National Commission on Digestive Diseases report and the scientific community's Challenges in IBD Research agenda, particularly as they relate to pediatrics.(p.101)

#### Action taken or to be taken

The NIDDK continues to maintain a significant and productive IBD research portfolio. The Institute is committed to engaging with the IBD community and remains attentive to the research goals outlined in the Crohn's and Colitis Foundation of America's research plan, "Challenges in Inflammatory Bowel Diseases Research." These goals align with those of the National Commission on Digestive Diseases.

The NIDDK IBD Genetics Consortium has used genome-wide studies to uncover over 50 genetic variants associated with either Crohn's disease and/or ulcerative colitis—the two major forms of IBD—in adult and pediatric populations. In one recent study from FY 2010, the Consortium carried out the largest genome-wide association study to date for identifying five new regions of the genome that increase children's risk of developing IBD. In addition to the five new genetic regions that are unique to early-onset IBD in children, the pediatric population also has many of the genetic risk factors previously identified in adults with IBD. In a second FY 2010 study, researchers from the Consortium identified at least 30 distinct genetic risk factors for ulcerative colitis. The function of genes located near these genetic variants highlight the importance of several biological pathways in the pathogenesis of ulcerative colitis. By identifying additional genetic variants associated with developing IBD, researchers will gain insight into the causes of these diseases and potentially develop strategies to help detect, treat, and prevent IBD.

Research on the genetic, cellular, and environmental factors that might contribute to the development of IBD was accelerated through support from the American Recovery and Reinvestment Act. ARRA awards were made to expand and develop resources of the IBD Genetics Consortium, identify additional rare genetic variants associated with IBD, study the biological processes mediating chronic inflammation in the intestines, understand how the cellular barrier lining the intestine contributes to disease, and develop novel methods for diagnosing and treating patients with IBD.

There is currently limited clinical information available to guide the treatment of ulcerative colitis in children. Through support from NIDDK, researchers are planning a

clinical trial called Predicting Response to Standardized Pediatric Colitis Therapy: The PROTECT Study. This trial will evaluate whether a combination of clinical, genetic, and immunologic tests can be used to predict response to standard medical therapy for children newly diagnosed with ulcerative colitis. The goal is develop a model to guide clinical decision-making and improve long-term outcomes.

#### Item

***Inflammatory Digestive Diseases in Children*** - Some inflammatory digestive diseases begin in childhood and progress through life. Examples include inflammatory bowel disease, gluten sensitive enteropathy, autoimmune enteropathy, necrotizing enterocolitis with resultant intestinal failure, acute and chronic pancreatitis, autoimmune hepatitis, autoimmune cholangitis, and primary sclerosing cholangitis. As more effective interventions in the pediatric age group could reduce the burden of these illnesses in children and adults, the Committee urges the NIDDK to encourage more research leading to earlier diagnosis and treatment of these and other digestive diseases that are lifelong burdens. (p. 101)

#### Action taken or to be taken

The NIDDK supports a broad portfolio of basic, clinical, and translational research on inflammatory digestive diseases in children. The objective of this research is to achieve a better understanding of disease mechanisms and to develop improved methods for diagnosing and treating these digestive diseases in children.

Researchers from the NIDDK Inflammatory Bowel Diseases (IBD) Genetics Consortium have recently carried out the largest genome-wide association study to date for identifying genetic variants associated with IBD in children. In this study comparing children with IBD and healthy children, the researchers identified variants in five new regions of the genome that increase children's risk of developing IBD. Defining the genetic variations that predispose children to developing IBD enables researchers to gain insight into the causes of these diseases and potentially develop new strategies to detect, treat, and prevent early-onset IBD in children.

The NIDDK-supported Childhood Liver Diseases Research and Education Network (ChiLDREN) is conducting studies on the causes, natural history, and treatment of pediatric cholestatic liver diseases. In these diseases, the blockage and loss of functional bile ducts due to genetic defects, inflammation, or other causes can lead to liver cirrhosis, liver failure, and liver cancer. The NIDDK is supporting research to test pharmaceutical agents for the treatment of primary sclerosing cholangitis and to identify the genetic and environmental risk factors associated with primary sclerosing cholangitis and its relationship to ulcerative colitis.

The NIDDK is also pursuing basic and clinical research on acute and chronic pancreatitis. In an ongoing study, NIDDK-supported investigators are carrying out a genome wide analysis to identify genetic risk factors associated with recurrent acute and chronic pancreatitis. Identification of genetic risk factors for these inflammatory diseases may be relevant to both the adult and pediatric populations. In addition, the

NIDDK actively engages with the research community to encourage investigators to submit applications for research on pediatric pancreatitis, and the Institute receives input from key stakeholders in the pancreatic disorders community through the NIDDK's National Advisory Council. While the NIDDK provides support for basic and clinical research on necrotizing enterocolitis, primary support for research on this inflammatory digestive disease in children falls within the mission of other Institutes and Centers at the NIH. The NIDDK has collaborated with the lead Institute on necrotizing enterocolitis research, the NICHD, as well as NIAID in supporting grants responsive to an initiative to stimulate research on new preventive and therapeutic approaches to necrotizing enterocolitis.

#### Item

***Interstitial Cystitis (IC)***-The Committees supports the important work of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain [MAPP] Research Network but encourages the NIDDK to continue to expand its portfolio specifically on IC research. (p. 101)

#### Action taken or to be taken

The NIDDK is continuing its commitment to research on the painful urologic condition interstitial cystitis/painful bladder syndrome (IC/PBS) through multiple avenues, including the MAPP Research Network and new initiative planning.

Complementing individual studies supported by the regular research portfolio, the multi-center MAPP Research Network continues to move forward on collaborative studies that may elucidate the causes and natural history of IC/PBS and thereby reveal new approaches to management, prevention, and treatment. For example, the Network has initiated the highly collaborative Trans-MAPP Epidemiology/Phenotyping Study. This project will examine how and why IC/PBS and other chronic urologic pelvic pain conditions develop and change over time, and whether there are differences that define unique subgroups of patients who may benefit from different treatment strategies.

Moreover, the MAPP Research Network recently developed an Ancillary Studies Program through which researchers not currently funded as part of the Network may initiate collaborative studies with Network investigators—thus leveraging this investment in research on IC/PBS and other urologic chronic pelvic pain conditions. The recently launched MAPP Research Network Web site (<http://www.mappnetwork.org/>) provides general information on the Network's goals and scientific activities, as well as information on how interested patients may get involved in Network studies. Funds from the American Recovery and Reinvestment Act were used to support an ancillary study that will collect data and samples from normal individuals to greatly help biomarker efforts within the MAPP network.

To expand its portfolio and further bolster IC/PBS-specific research, the NIDDK is also planning a new initiative in this area for FY 2011, the purpose of which will be to support interdisciplinary research focused on IC/PBS. NIDDK will also continue to encourage

investigators to submit relevant applications and seek to identify important studies to support as part of its regular efforts to promote IC/PBS research.

Item

***Irritable Bowel Syndrome (IBS)*** - The Committee encourages the NIDDK to consider collaborating with the IBS patient and scientific community to host a state of the science conference focusing on recent breakthroughs in the etiology and epidemiology of IBS. (p. 101)

Action taken or to be taken

The NIDDK is pleased to work closely with patient and scientific professional groups to develop potential topics for future scientific meetings or workshops. The NIDDK supports a strong portfolio of basic and clinical IBS-related research projects, many of which reflect previous discussions with those groups. For example, the Center for Neurovisceral Sciences and Women's Health is supported by a Specialized Center of Research grant that is co-funded by the NIH Office of Research on Women's Health and the NIDDK. The primary focus of the Center is research on the manifestation and treatment of IBS and interstitial cystitis. A recent Center-supported clinical research study of female patients with IBS demonstrated structural changes in specific brain regions, which included both decreases and increases in key areas of the brain related to attention, regulation of emotions, pain inhibition, and the processing of visceral information. These findings are particularly significant because discovery of these structural changes, in addition to the previously known gastrointestinal functional changes associated with IBS, supports the concept that IBS is a "brain-gut" disorder, which will have implications for developing therapies.

Item

***National Commission on Digestive Disease***- The Committee requests a progress report on implementing recommendations in the Commission's final report issued in March 2009. This report should be included in the NIDDK's annual report and include the NIDDK digestive disease research funding history over the past 3 years. (p. 101,102)

Action taken or to be taken

The Commission's digestive diseases research plan was a report to the NIH Director, representing a large effort by the external research community and trans-NIH representatives, which includes broad and numerous research recommendations (<http://www2.niddk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/FinalResearchPlanPosting.htm>). The research plan was developed and is being actively implemented by multiple Institutes, Centers, and Offices across the NIH, as well as other Federal and non-Federal partners involved in digestive diseases research.

As one of the NIH components participating in development and implementation of the Commission's research plan, the NIDDK is implementing research recommendations in the plan, including applying all available forms of research support to address promising research directions. For example, the NIDDK is supporting a new Hepatitis B Research

Network to advance understanding of disease processes and natural history, as well as to develop effective approaches to treatment. The Institute is also continuing to support the adult and pediatric Acute Liver Failure Study Groups, as well as the Drug-Induced Liver Injury Network and Nonalcoholic Steatohepatitis Clinical Research Network, to conduct multi-center clinical research on these liver-related conditions. A new multi-center clinical study is being planned to conduct a long-term trial of standard medical therapy in children with ulcerative colitis that will improve outcomes for these children by developing models to inform individualized treatment plans. The NIDDK has also published some new initiatives to solicit digestive diseases research, including the establishment of an Intestinal Stem Cell Consortium, which is based on the Commission's recommendation to "develop new technologies to isolate, characterize, cultivate, and manipulate stem cells of the digestive system."

Recent advances in digestive diseases research supported by the NIDDK, which is responsive to the Commission's recommendations, include: uncovering new genetic risk factors associated with inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, in both adults and children; discovering how gut microbes influence immune responses and intestinal inflammation; identifying genetic risk factors for celiac disease; performing successful implantation of a bioengineered anal sphincter in mice, which may form the foundation for therapy of fecal incontinence; demonstrating benefits of therapies for adult nonalcoholic steatohepatitis and early-stage acute liver failure; and finding new therapeutic approaches to genetic liver diseases, such as alpha-1 antitrypsin deficiency and hereditary tyrosinemia.

Funding for NIDDK digestive disease research over the most recent 3 fiscal years for which final data are available was: \$331 million (FY 2007), \$364.9 million (FY 2008), and \$414.1 million (FY 2009).

#### Item

***Pediatric Kidney Disease*** - Because many adult kidney diseases originate prenatally or during childhood, the Committee encourages the NIDDK to assign a higher priority to pediatric kidney disease research, especially congenital kidney abnormalities, pediatric glomerular disease, pediatric acute kidney injury, and pediatric chronic kidney disease. Due to the unique challenges of recruiting children into clinical trials, an emphasis on funding for both infrastructure and collaborative registries to enhance comparative multicenter pediatric prospective clinical/translational trials that will improve patient outcomes is strongly encouraged. (p. 102)

#### Action taken or to be taken

The NIDDK has taken several actions to address the important problem of kidney disease in children and adolescents. The Institute has expanded investment in the two ongoing studies of pediatric kidney disease. An ancillary study to the Chronic Kidney Disease in Children (CKiD) study received additional funding to investigate genetic factors associated with progression of kidney disease in this population. The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial was extended for an additional three years. Additionally, funds from the American Recovery

and Reinvestment Act were used to support a large ancillary genetics study to RIVUR that will evaluate the genetic variations in the development of vesicoureteral reflux and the risk for developing long-term morbidity.

The NIDDK also supports robust research efforts into the problem of pediatric glomerular disease. The NIDDK, along with NIH Office of Rare Diseases Research and the NephCure Foundation, also supports the Nephrotic Syndrome Rare Disease Clinical Research Network. It is a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of three glomerular diseases: minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy. The researchers are investigating the underlying disease mechanisms and assess the responsiveness of these diseases to various treatment approaches. This Consortium provides a readily accessible research and education resource that will significantly advance the study, classification, characterization, diagnosis, and treatment of these diseases. It also brings clinical and translational scientists together with lay research and patient foundations to educate patients with these diseases. Patient recruitment has begun for this study.

The NIDDK is also concerned about kidney and urologic stone disease in pediatric patients. The Institute has established a Consortium for Hereditary Causes of Nephrolithiasis and Renal Failure to study primary hyperoxaluria, cystinuria, APRT deficiency, and Dent disease. These four diseases are characterized by deposition of crystals in the kidneys that often lead to kidney stones. The Consortium facilitates cooperative exchange of information and resources among investigators, clinicians, and patients, and researchers in order to improve care and outcomes for patients with rare stone diseases. It will focus on the discovery of biomarkers of disease risk, disease activity, and response to therapy for these four rare diseases that share similar mechanisms and severe disease manifestations. Finally, the Institute is moving forward with the “Kidney Research National Dialogue,” an effort to strategically plan its future research focus for kidney disease, including pediatric kidney disease. It is expected that a National Blueprint for Kidney Disease Research will be ready in mid-2011.

#### Item

***Polycystic Kidney Disease (PKD)***- The Committee applauds the NIDDK's commitment to the CRISP and HALT-PKD clinical studies, the four PKD Centers of Excellence, research grants supporting the development of PKD biomarkers, high-throughput screening assays, and additional PKD specific translational research. The Committee suggests that the NIDDK's strategic plan for PKD complement current public/private partnerships such as the FDA partnership designed to speed the development of PKD therapies to market and the establishment of PKD diagnostic and clinical treatment centers in collaboration with the NIH. To expand and solidify this integrated approach, the Committee urges the NIDDK to consider sponsoring an international PKD strategic planning meeting. (p. 102)

#### Action taken or to be taken

Two large NIDDK-funded studies of PKD—HALT-PKD and CRISP—are focused on identifying better monitoring and imaging approaches as well as improvements in patient care for individuals with the most common form of PKD. The Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments. The image analysis methods developed in CRISP are currently being implemented in HALT-PKD and have been implemented by industry-sponsored trials for patients with PKD.

The HALT-PKD study has been extended to demonstrate the validity of total kidney volume and other biomarkers as surrogates for progression of disease and to test the blockade of the renin-angiotensin system as a therapy for PKD.

The NIDDK has supported extensive and ongoing data collection related to volumetric analysis of kidney images, PKD genotyping, and surrogate marker analysis in the HALT-PKD and CRISP studies. These data and samples will be available to the research community through the NIDDK Repository ([www.niddkrepository.org](http://www.niddkrepository.org)).

Four recently funded PKD Research and Translational Centers will perform basic and clinical research to develop and test additional promising therapies. The purpose of the Centers is to provide resources for communication and collaboration between basic and clinical researchers in the field of PKD. The shared resources will enhance the efficiency of research and foster collaborations with and among institutions with strong existing PKD research programs. In order to promote integration and coordination of efforts across the research spectrum, the NIDDK expects to plan a conference in late FY 2011 of the PKD Centers, HALT-PKD, and CRISP investigators, and other interested researchers to discuss latest findings, to share resources, and to integrate efforts in this field to speed the discovery of new and effective therapeutic approaches to PKD. The NIDDK is also planning to hold an international meeting to explore potential worldwide collaborations in PKD research. The NIDDK considers collaborations as key to success in treating this disease.

In addition to these efforts, a new NIDDK initiative is encouraging identification and validation of biomarkers and risk assessment tools for kidney function, injury, and disease progression in people with chronic kidney disease. Improved biomarkers for screening, monitoring kidney function, and managing chronic kidney disease would be of benefit to people with PKD. With regard to public-private partnerships, the NIDDK is working with the FDA and private partners to develop a disease model that will facilitate development of novel therapies for PKD. Finally, the Institute is moving forward with the “Kidney Research National Dialogue,” an effort to strategically plan its future research focus for kidney disease, including PKD and pediatric kidney disease. It is expected that a National Blueprint for Kidney Disease Research will be ready in mid-2011.

#### Item

***Vitamin D and Chronic Kidney Disease*** - The Committee encourages support for research on the relationship between vitamin D and morbidity and mortality in chronic kidney disease. Research is also needed on the value of anti-resorptive therapies, the link between renal insufficiency and diabetic bone disease, the differences in calcification of blood vessels, the mechanisms of metastasis of renal cell carcinoma, and diseases that occurs in patients with end stage chronic renal disease on hemodialysis. (p. 102)

#### Action taken or to be taken

NIDDK recognizes the importance of Vitamin D to the morbidity and mortality of patients with chronic kidney disease (CKD).

The Institute currently supports research investigating the role of vitamin D in chronic renal insufficiency. Furthermore, an NIDDK-supported randomized ancillary clinical trial is assessing whether vitamin D supplementation prevents the development and progression of diabetic kidney disease. With respect to conditions which predispose people to forming defective bone tissue, NIDDK supports research to develop non-invasive detection methods to monitor bone health. The Institute continues to fund studies to understand the mechanisms of vascular calcification in the setting of CKD. Specifically, the Chronic Renal Insufficiency Cohort (CRIC) Study is examining coronary artery calcification prospectively in patients with chronic kidney disease. NIDDK is well aware of the increased risk of cardiovascular disease in patients with end-stage renal disease and supports research studies to address this important issue.

Finally, the Institute is moving forward with the “Kidney Research National Dialogue,” an effort to strategically plan its future research focus for kidney disease, including chronic kidney disease. It is expected that a National Blueprint for Kidney Disease Research will be ready in mid-2011.

## National Institute of Neurological Disorders and Stroke (NINDS)

### Senate Significant Items

#### Item

***Charcot-Marie-Tooth (CMT)*** - The Committee commends the NINDS for its recent efforts to advance understanding and development of therapies for CMT and related neurodegenerative diseases. The Committee supports translational research that has the greatest potential to rapidly develop therapies for patients with CMT and other degenerative disorders. The Committee encourages the NINDS to develop innovative communications mechanisms to ensure that information on treatments can be shared in an accurate and timely manner with practitioners and patients.(p.102)

#### Action taken or to be taken

Scientists have made much progress in recent years in understanding the mechanisms that cause Charcot-Marie-Tooth disorder (CMT) and it is therefore an ideal time for research to move toward therapy development. The CMT Association (CMTA) has launched an important effort in this regard, the “CMTA Strategy to Accelerate Research (CMTA STAR).” One of the first goals of the project is to use high-throughput screening to identify compounds that could potentially be used to treat CMT1A, the most common type of CMT and one for which the underlying mechanisms are well understood. In a partnership with the NIH National Chemical Genomics Center (NCGC), the project has completed screening a CMT1A cell line (cells that express PMP22, the gene that is over-expressed in patients with CMT1A) against more than 3500,000 compounds – including some FDA approved drugs - in the NCGC’s library. A number of “hits” have already been identified and these compounds may warrant development as therapeutics following additional screening and testing in mouse models of CMT1A.

In addition, NINDS also funds research aimed at developing therapies for CMT. Using funds provided to NIH through the American Recovery and Reinvestment Act of 2009 (ARRA), NINDS funded a “Challenge Grant” to identify potential compounds to treat CMT2E. This form of CMT is caused by mutations in a gene encoding a structural protein found in neurons. The mutation results in improper aggregates or clumps of the protein. The project aims to identify small molecules that can prevent this incorrect assembly of the protein and to develop an animal model to test these compounds. In August 2008, NINDS and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), released a pair of initiatives as part of the “Cooperative Program in Translational Research for Neuromuscular Disease” to encourage therapy development for neuromuscular disease. Through this program, NINDS recently funded a project for preclinical studies to test the feasibility of using gene delivery of a growth factor gene to treat CMT1A. NINDS continues to encourage CMT researchers to apply for funding through this program. NINDS also funds the Inherited Neuropathies Consortium, one of the Rare Disease Clinical Research Networks, which brings together clinical researchers with expertise in CMT. The activities of the Consortium are aimed at ensuring that the field is poised to conduct clinical trials when potential therapies reach

that point. In support of this goal, NINDS recently awarded a \$100,000 supplement to the Consortium to fund the development of an international registry.

While dissemination of therapies is premature at this point, NINDS program officers work closely with the CMT Association and CMT researchers to promote therapy development projects. An NINDS program director serves an advisory role in CMTA STAR; it is hoped that after the initial screening stage of the project, the researchers can apply to the NINDS Cooperative Program in Translational Research with a proposal for developing one or more of these compounds to the point of an Investigational New Drug (IND) application. NINDS program staff are also participated in a CMT Association workshop in November 2010 to discuss therapy development process for CMT type 2A. As new therapies are developed, NINDS will work closely with the CMT Association and other relevant patient voluntary groups as well as professional organizations to ensure that information about these new treatments are readily communicated with patients and providers.

#### Item

**Epilepsy** - The Committee applauds the NINDS for recognizing epilepsy as a priority area and for developing new research opportunities that will accelerate the rate at which research will be conducted. Following on the heels of the Curing Epilepsy 2007 Conference that resulted in community-determined benchmarks designed to forward the progress of finding a cure for epilepsy, these new grant opportunities will provide avenues for cooperative programs in translational research and high-risk transformative research programs designed to yield new information about epilepsy. The Committee continues to be particularly interested in three areas of epilepsy research- epileptogenesis, co-morbidities, and sudden unexplained death-and encourages the NINDS to focus attention on existing and new grants and mechanisms to address these areas. (p. 102,103)

#### Action taken or to be taken

To accelerate progress toward better treatment or prevention of the epilepsies and their associated comorbidities, NINDS has recently developed a set of initiatives for new epilepsy research programs. For approximately one-third of people with epilepsy, available treatments do not provide adequate seizure control. In March 2010, NINDS issued funding announcements for translational research to develop new and better therapies for such treatment-resistant epilepsy and for the prevention of epileptogenesis, the process that leads to chronic, spontaneous seizures. NINDS also solicited applications for a new Epilepsy EUREKA program that will support innovative and potentially transformative epilepsy research to understand better the disease mechanisms and identify new strategies for treatment or prevention. Finally, NINDS will soon issue the first of a series of announcements for Epilepsy Centers without Walls for collaborative research. The program will support multidisciplinary consortia to solve specific challenges in the prevention, diagnosis, or treatment of the epilepsies and related comorbidities. The Centers will bring together the best investigators, regardless of geographic location, and are a novel approach to addressing difficult research needs. NINDS anticipates that the first Centers will focus on epilepsy genetics, sudden

unexpected death in epilepsy (SUDEP), and the prevention of epileptogenesis. To inform the development of these Centers and the selection of their research challenges, NINDS held two scientific workshops in August and September 2010 focused on the development of antiepileptogenic interventions and on human epilepsy genetics.

In addition to these new programs, whose funding will begin in FY2011, NINDS supports research on epileptogenesis, comorbidities, and SUDEP through investigator-initiated research and other existing programs. The Epilepsy Research Benchmarks also emphasize and encourage research in these areas, reflecting their importance within the epilepsy research community.

Ongoing NINDS funded research on epileptogenesis includes a longitudinal study of 200 children to clarify the relationship between prolonged febrile seizures in childhood and the development of chronic temporal lobe epilepsy. A range of other basic and clinical studies are investigating epileptogenic mechanisms associated with brain malformations, genetic defects, and insults that increase the risk for epilepsy, such as traumatic brain injury (TBI), neonatal oxygen deprivation, stroke, or infection. This research is pointing to changes in brain circuits and signaling pathways that may be targeted to prevent epilepsy in people at risk. The emergence of seizures after a precipitating insult may occur gradually over many months or years, which limits the feasibility of screening and testing interventions. Two newly funded projects, using new animal and in vitro models for large-scale antiepileptogenic drug screening, offer a more practical approach to identifying promising leads. Beyond seizures, NINDS also supports research on cognitive deficits, depression, and other comorbid conditions in epilepsy. This includes, for example, clinical research and studies in animal models on shared mechanisms in depression and epilepsy and on the neuropsychological and cognitive consequences of recurrent childhood seizures. NINDS-supported research on SUDEP led recently to the identification of potential risk factors and biological mechanisms linking epilepsy and cardiac dysfunction. In addition, NINDS is collaborating with the CDC to hold an upcoming workshop to consider the feasibility and design of a mortality surveillance system for epilepsy to determine better the prevalence of SUDEP and to identify associated factors.

#### Item

**Frontotemporal Dementia** - The Committee commends the NINDS and NIA for establishing a frontotemporal dementia [FTD] module of the Uniform Data Set [UDS] , with data collected in a uniform manner across the Alzheimer's Disease Centers [ADCs] and maintained within the National Alzheimer's Coordinating Center database. The Committee encourages the two Institutes to establish a pilot program of FTD core centers within the existing ADCs to characterize and follow patients with FTD longitudinally in order to prepare for participation in drug trials. (p.103)

#### Action taken or to be taken

The NINDS and the NIA have been working together to develop a common clinical data set for frontotemporal dementia (FTD) to facilitate clinical research and drug discovery. To inform this effort, the NINDS, the NIA, and the Association for Frontotemporal

Dementias held a workshop in February of 2010 where experts in the field discussed ways to establish standard data collection protocols, FTD-specific data elements, and a plan for integrating FTD data into the National Alzheimer's Coordinating Center (NACC) data repository. The initial draft of this common data module is complete, and plans for pilot studies using the data set will be discussed at another workshop, the FTD International Research Workshop, to be held in October of 2010. The pilot studies will include three to four Alzheimer's disease Centers (ADCs) that are currently treating FTD patients, and are expected to be completed in early 2011. Also to be discussed at the upcoming workshop is a timeline for validation of the neuropsychology assessments specifically designed for the FTD module. The NINDS and the NIA are contributing additional funds for this validity testing, and training will be provided by the NACC staff to the ADCs involved in FTD research once the module is complete. The FTD module and the infrastructure in place at the ADCs provide investigators with tools to accelerate clinical research in FTD. It is anticipated that applications capitalizing on these resources will be submitted to the NIA and the NINDS in 2011.

The NINDS and the NIA also co-fund other initiatives that aim to support infrastructure to better prepare the field for conducting clinical trials to test emerging therapies for FTD. One project utilizes the infrastructure established by the Alzheimer's disease Neuroimaging Initiative. Brain images of FTD will be studied in order to determine the best imaging modalities for following FTD in patients over time. This research will facilitate planning of clinical trials with the use of brain imaging to help investigators decide which drugs may show the most promise for treating FTD.

The NINDS supports multiple efforts to facilitate clinical, basic, and translational research in FTD. One clinical study funded by the NINDS in 2010 will illuminate the complex neural processes that are thought to underlie language deficits in FTD patients and in patients with corticobasal degeneration (CBD) that affect their ability to process numbers. Another grant, co-funded by the NINDS and the NIA, provides funding for a program in which a highly integrated group of clinical and basic scientists will work together with patients, post-mortem tissue, and animal model systems to understand better the etiology and development of disease characteristics present in both amyotrophic lateral sclerosis (ALS) and FTD patients. The NIA supports a program project grant designed to determine the imaging, emotional, social-cognitive, language, genetic and diagnostic features of FTD and related disorders including CBD, progressive supranuclear palsy and ALS in contrast to Alzheimer's disease and healthy aging.

#### Item

***Spinal Cord [Brachial Plexus] and Peripheral Nerve Injuries*** - The Committee encourages research support into the pathophysiology of spinal cord, brachial plexus, and peripheral nerve injuries in order to develop targeted therapies to improve neural regeneration and functional recovery. (p. 103)

#### Action taken or to be taken

NINDS supports extensive research to understand the pathophysiology of spinal cord, brachial plexus, and peripheral nerve injuries and to develop targeted therapies to promote regeneration and restore function. Each type of injury presents special challenges.

The spinal cord, like the brain, is part of the central nervous system (CNS), and the CNS shows very limited spontaneous self-repair after injury. Researchers have discovered factors responsible for the lack of recovery in the spinal cord, including limited readiness of CNS nerve cells to grow as well as inhibitory molecules in spinal cord tissue that restrict growth. Degeneration of non-nerve cells that support nerve fibers is also a key factor in functional deficits. NINDS supports extensive research building on these insights to foster recovery, including the use of natural growth factors to promote nerve fiber regeneration, development of interventions to overcome growth inhibitors in the spinal cord, and cell transplantation to replace lost supporting cells.

Peripheral nerves regrow more readily following injury than CNS nerve fibers, however growth is slow and the peripheral nerve fibers may not reconnect to the proper targets to restore function. When injuries are minor and neurosurgeons can connect damaged nerves without tension, regeneration and functional recovery can take place through the original nerve. More severe injuries may require grafting of a nerve scaffold to guide nerve growth. Researchers are developing methods to prevent rejection of nerve grafts without the use of powerful immunosuppressants that are now necessary, thereby increasing the safety and expanding the use of this approach. Another strategy under investigation is the use of artificial scaffolds derived by nanotechnology or tissue engineering techniques to support nerve growth. Pathophysiological studies have also led to recognition of nerve tissue reactions to injury that limit recovery, and interventions are under development to counteract these reactions. Other research on peripheral nerve injuries uses natural growth promoting factors to accelerate and guide regeneration, rehabilitation exercises that encourage nerve fibers to grow and reconnect properly, and insights about molecular changes in nerve cells following injury to prevent chronic pain.

Injuries to the brachial plexus, through which nerves of the upper extremities connect to the spinal cord, also present special challenges. Following damage to the spinal roots, nerve fibers may regenerate in the root but not cross into the spinal cord because CNS tissue inhibits growth. Insights from both spinal cord injury and peripheral nerve injury are relevant to brachial plexus injuries. The NINDS also supports research specifically directed at brachial plexus injuries, including the use of natural growth promoting molecules and tissue engineering strategies to overcome this barrier.

Several cross cutting areas of active NINDS research have a bearing on all of these injuries. Among these are extensive research on the basic biology of nerve growth, how nerves find proper connections during development and regeneration, how acute pain becomes chronic pain, tissue engineering and biomaterials science to promote regeneration, and an extensive program, ranging from engineering to human testing, to develop neural prosthetic devices to restore function lost by injury.

#### Item

***Spinal Muscular Atrophy (SMA)***- The Committee is concerned that the declining NIH investment in developing treatments for SMA comes at a time when treatments are closest to the clinic and the community will benefit from NIH support most. When SMA was designated by NIH in late 2003 as the model disease for a therapeutics development program (the SMA Project), it was viewed as an unprecedented opportunity to find treatments for this devastating and relatively common childhood disease. The Committee strongly supported this NINDS-initiated program to enable the development of therapeutic candidates for the treatment of SMA. Since then, the Committee understands that research supported by private voluntary organizations and the NINDS SMA Project have led to multiple potential treatments for SMA that are advancing rapidly through the drug development pipeline, with the most promising drug candidates expected to reach the clinical trials stage within 12 months. To complete development of any of these potential new treatments, NIH support is needed to put into place the infrastructure for clinical trials. The Committee requests an update in the fiscal year 2012 congressional budget justification. (p. 127)

#### Action taken or to be taken

NIH commitment to SMA has been and remains strong. NIH has aggressively increased support for preclinical development of treatments for SMA and is also launching a new program to provide the infrastructure for clinical trials of novel therapies for SMA and other neurological disorders for which promising treatments are now emerging.

The NIH supports preclinical development of drug, cell, and gene therapies for SMA through multiple investigator-initiated and targeted programs. The SMA Project is making encouraging progress. NINDS has applied for two patents covering promising compounds from the Project, and preclinical safety testing is underway with the goal of readiness for clinical trials by the end of 2011. Because the failure rate at each stage of drug development is very high for all diseases, the Project is continuing to develop other drug candidates, and NIH supports several complementary preclinical development efforts. NINDS has funded a major new SMA drug therapy development project through a targeted solicitation for applications to the Institute's milestone-driven Cooperative Program in Translational Research. The NINDS and the NICHD have each funded new therapy development projects through investigator-initiated grant programs as well, and the NIH Chemical Genomics Center is also supporting drug screening for SMA. Other newly funded grants include a multi-investigator program project grant to understand SMA mechanisms and identify additional targets for therapy development. American Recovery and Reinvestment Act funds enabled the NIH to increase support for SMA research through major investments in gene therapy and cell-based approaches, as well as research to improve understanding of SMA.

Because therapies for SMA and several other neurological diseases are advancing toward readiness for clinical testing, NINDS is developing a program to expedite early-phase clinical trials. Rather than developing separate clinical networks for each

disease, the Network for Excellence in Neuroscience Clinical Trials (NEXT) will jointly serve SMA and other neurological diseases. The program will be open to the best candidate therapies whether they arise from NIH programs or other sources. For many reasons, this combined network will be more cost effective and efficient than separate networks for each disease. This network will offer expertise in a range of disciplines, including pediatrics, and provide the SMA community with access to a breadth of experience in running clinical trials. In September 2010, notices informed the research community that the NINDS will issue Requests for Applications (RFAs) to fund a data coordinating center, a clinical coordinating center, and multiple clinical sites. NIH also continues to prepare for clinical trials in other ways. The NICHD, for example, supplements the development of both newborn and carrier screening tests for SMA, which will be critical for the success of clinical trials in infants, and research on quantitative testing of muscle strength in SMA that will be a key outcome measure in clinical trials of therapies for adults and children.

Finally, NIH not only continues to coordinate SMA research internally but also works closely with the private sector and the advocacy community. For example, in fall 2010, NINDS, NICHD, and NHGRI held a workshop involving public and private sector researchers and advocates working toward SMA therapy development. This workshop examined ongoing preclinical and clinical efforts in therapy development to improve their efficiency and effectiveness.

#### Item

**Stroke** - The Committee is concerned that the NIH continues to invest only 1 percent of its budget on stroke research, recognizing that funding and resources for this often deadly and disabling disease is not commensurate with current scientific opportunities, the number of Americans afflicted, the increasing prevalence of stroke in an aging population, and the economic toll it exacts on our Nation. In light of the exorbitant burden that stroke places on our society now and in the future, the Committee urges the NIH to aggressively expand and intensify its investment in basic, translational and clinical stroke research to capitalize on advances and burgeoning scientific opportunities. (p.103)

#### Action taken or to be taken

The NINDS, the lead institute for stroke research at the NIH, recognizes the enormous burden stroke places on society and invests more than 10 percent of its budget, which exceeds spending in any of the other 600 neurological disorders in the NINDS portfolio, on research to understand better, prevent, and treat stroke. The NINDS supports a large and broad portfolio of stroke research that spans the spectrum from basic and translational studies to large Phase III clinical trials.

NINDS supports a research network, Neurological Emergency Treatment Trials (NETT), through which a number of stroke trials are conducted. The streamlined infrastructure and design of NETT promotes efficiency and facilitates clinical studies during the very narrow window of opportunity for treatment that is relevant to many acute neurological disorders, including stroke. One ARRA-funded trial will utilize NETT to determine

whether administration of aspirin and clopidogrel, a drug that prevents clot formation, can reduce the 90-day risk of stroke in patients who have had a transient ischemic attack compared to treatment with aspirin alone. Another recently approved clinical trial will also use NETT to determine the best approach for managing blood glucose in stroke patients who present with hyperglycemia. In addition, the NINDS also supports stroke research through its Specialized Program of Translational Research in Stroke (SPOTRIAS), a network of research centers across the country that is focused on improving management and outcomes of acute stroke.

The NINDS and NHLBI often collaborate on studies that aim to address common vascular risk factors relevant for both heart disease and stroke. Examples of such collaborations include a large trial examining whether controlling blood pressure to levels below what is recommended by current guidelines would further reduce the risk of stroke, heart attack or cognitive decline. Other examples include an epidemiology study designed to investigate the natural history and cause of atherosclerosis, a known risk factor for both heart disease and stroke, and a cohort study to investigate the prevalence and development of vascular disease in U.S. Hispanics.

NINDS' efforts to identify stroke risk factors also include genome-wide association studies (GWAS) in which DNA samples are evaluated in order to identify genes associated with elevated risk for stroke. One NINDS-supported GWAS project will recruit 6,000 people to understand risk factors for intracerebral hemorrhage (ICH), the most fatal form of stroke for which African Americans and Hispanics have double the risk compared to whites. This study will also assess differences in brain imaging and outcome of ICH by race/ethnicity.

Tissue plasminogen activator (tPA) is the only FDA-approved treatment for acute ischemic stroke. However, there are little data on the use of tPA in children. Although childhood stroke is relatively uncommon, over 75% of children with acute stroke will suffer long-term neurological deficits, epilepsy or death. The NINDS is supporting efforts to investigate safety and dosing of tPA in children in hope of providing this important population access to an effective treatment for stroke.

The NINDS Stroke Progress Review Group (SPRG) developed priorities for the field nearly 10 years ago, and published an interim report in 2006. The NINDS is initiating an effort to re-assess progress that has been made in the field, and to take a fresh look at research needs for the future. This process will help the NINDS prioritize opportunities for expanded investments in basic, translational, and clinical stroke research.

#### Item

**Stroke in Women** - Many studies have shown significant gender differences concerning stroke. For example, women often receive fewer diagnostic tests and intervention procedures; women have a much higher rate of death from brain aneurysms; and hormone replacement therapy and oral contraceptives increase risk of stroke. The Committee encourages the NINDS to give specific attention to gender-related differences in stroke risk, preventative measures, acute stroke management,

post-stroke recovery, long-term outcomes, and quality of care. Also of particular concern is the underrepresentation of women in many NIH-sponsored trials of stroke. (p. 103)

#### Action taken or to be taken

The NINDS supports a large and broad portfolio of stroke research that includes multiple efforts to increase understanding and address the substantial burden that stroke places on women better.

Multiple NINDS-supported research studies aim to understand the physiological basis for gender-related differences in stroke risk and outcomes. One study funded by the NINDS and the NHLBI will follow a cohort of women to identify biological and physiological markers associated with ischemic stroke in women, and to establish which of those are influenced by sex hormones and/or menopausal status. This study is expected to inform future development of gender-specific predictors for stroke risk in women. In another study, investigators will explore how biological functions programmed by sex-specific genes are related to gender differences observed in fundamental cell death pathways that are activated by a stroke. The NINDS is also funding a study to investigate the physiological basis and role of estrogen receptors in gender-related differences in incidence of stroke associated with cardiovascular surgical procedures. Additionally, several NINDS-funded translational research studies are evaluating promising new stroke therapies in both male and female animals.

The NINDS supports a number of surveillance studies that aim to illuminate differences in stroke knowledge, risk and outcomes among different sub-populations, including women, in order to inform development of tailored prevention intervention strategies. For example, the Reasons for Geographical and Racial Differences in Stroke study (REGARDS) is a large cohort of over 30,000 participants, over half of which are women. This comprehensive assessment of disparities in stroke risk and incidence is one of the largest longitudinal cohort studies of African Americans and the only national study of the epidemiology of cognitive change. The large representation of women in this important population-based study is significant as it allows for data analyses of gender-specific differences, in general as well as among different racial populations. For example, a recent publication from this study revealed that evaluation of markers for inflammation led to more accurate vascular disease risk stratification, particularly in blacks and women, since they are at higher risk for increased levels of this marker. Studies from REGARDS will continue to improve our understanding of differences in stroke risk among a diverse U.S. population.

The NINDS supports a large number of clinical studies to improve acute management and long-term outcomes in stroke. All of NIH-funded clinical trials are required to set and justify target enrollment by race, ethnicity, and gender and to report on enrollment progress. Approximately half of the participants in all of the NINDS-supported stroke clinical trials are women so that data can be analyzed for gender-specific differences. These trials are investigating new approaches to treat acute stroke and brain hemorrhage, to reduce brain damage due to stroke and to improve rehabilitation

strategies, which will provide all patients, including women, and their physicians with more therapy options and a better chance of survival and recovery after a stroke.

#### Item

**Stroke Rehabilitation** - The Committee is pleased that the NINDS has convened an expert panel to discuss issues related to stroke treatment and recovery and how people reintegrate into their daily lives following a stroke. Given that stroke produces a substantial financial and emotional stress on the caregiver who is more often than not the female companion, wife, or daughter, the Committee encourages the NINDS to support studies that address the long-term consequences of stroke on the family and quality of life. (p. 103,104)

#### Action taken or to be taken

The NINDS recognizes that improving recovery in stroke survivors is a crucial element in the effort to reduce the burden of stroke on society. The NINDS supports a number of activities to ameliorate the long-term effects of stroke on the quality of life of its survivors and their families.

The NINDS is funding a study to address the psychosocial impact of stroke on family caregivers. The project aims to understand how stroke affects depression, physical health, health care access and use, and quality of life in primary caregivers identified from the Reasons Geographic and Racial Differences in Stroke (REGARDS) study. The project will also assess how depression, quality of life, and stressfulness experienced by the caregiver can impact the physical and emotional recovery of the stroke survivor. Results of this study will inform efforts aimed to improve recovery of stroke survivors and the well being of their caregivers.

NINDS-funded basic research related to stroke rehabilitation includes a study which aims to understand better the mechanisms of movement sensation in order to optimize the AMES (Assisted Movement with Enhanced Sensation) device, which was developed to repair sensory-motor connections in the brains of stroke patients. Another study is using an animal model to understand how stimulation of brain cells in the cortex promotes functional recovery. One grant the NINDS awarded with American Recovery and Reinvestment Act (ARRA) funds is investigating how brain functions that translate movement intentions into signals that initiate muscle action change after a stroke. The results of this work will improve rehabilitation strategies, including the design of assistive devices that interface with the brain.

The NINDS and the NICHD are co-funding two clinical trials in stroke rehabilitation. One trial is being conducted in community-based hospitals to assess whether treadmill training is more effective than a non-specific exercise regimen in improving walking ability after a stroke. In another trial, investigators will compare individualized task-based arm therapy with two standard arm therapy approaches. In an NINDS ARRA-funded clinical research study, investigators will use electronic medical records to compare outcomes of therapy in stroke patients to determine which post-acute care environments are most effective. These studies will help guide best clinical practices for stroke therapy.

The NINDS also co-funds with NICHD a research network focused on application of neural engineering techniques for rehabilitation strategies for disabling neurologic conditions. One project in this network, called Machines Assisting Recovery in Stroke, has established core research facilities for the development, testing, and application of robotic devices designed to help stroke survivors regain lost function. Another project involves clinical evaluation of brain stimulation used in conjunction with intensive therapy to improve recovery after stroke.

In 2009 the NINDS, NICHD, NIA and NIDCD organized a workshop in which investigators came together to discuss issues related to clinical and basic post-stroke rehabilitation research. In 2010, the NIH hosted another workshop to discuss ways to improve the ability of older adults, including stroke survivors, to live independently through the use of technology, which may serve to identify disease, help patients cope with impairment, and facilitate rehabilitation, exercise, and caregiver support. This workshop was sponsored by the NIA, NIBIB, NCRR, NICHD, NINDS, and OBSSR, and participants included investigators, clinicians, engineers, caregivers, patient advocates, and members from other federal agencies such as AHRQ, VA, FDA, NSF, and CMS.

## National Institute of Allergy and Infectious Diseases (NIAID)

### Senate Significant Items

#### Item

**Chronic Hepatitis B** - The Committee understands that while there are now a number of medications approved for the treatment of hepatitis B, they are of limited therapeutic value since they mostly target the same virus functions. The Committee urges additional research on different courses of treatment as well as ways to support efforts to identify new cellular and antiviral targets and develop new strategies for intervention. The Committee also urges an increased focus on pregnant women and pediatric cases of hepatitis B. (p. 104)

#### Action taken or to be taken

Hepatitis B virus (HBV) is responsible for the majority of the worldwide hepatitis burden, with chronic HBV-related cirrhosis and liver cancer causing over 3,000 deaths in the United States and about 1.2 million deaths worldwide each year. Research to develop new classes of drugs that are safe and effective in treating HBV infections remains a priority for NIAID. Through both solicited research programs and investigator-initiated research, NIAID-supported researchers are exploring novel viral targets for the development of classes of antiviral drugs for HBV that work by different mechanisms than currently licensed HBV polymerase inhibitors. While NIAID research on novel HBV therapies is still in early and preclinical development, the goal is to develop candidate therapeutic drugs that will treat chronic HBV infection in affected populations, including pregnant women and pediatric populations.

For example, NIAID supports a number of research grants to conduct basic research and to develop novel therapies for HBV. NIAID-supported researchers are at the early stages of developing therapies that target the HBV surface antigen, viral capsid, HBV covalently closed circular DNA (cccDNA) as well as the host's innate immune system. In FY 2011, NIAID plans to fund collaborative partnerships through the Partnerships for Development of New Therapeutic Classes for Select Viral and Bacterial Pathogens initiative. These partnership awards will help advance the development of new classes of therapeutic drugs for HBV.

NIAID also offers a broad array of preclinical and clinical research resources and services to researchers in academia and industry. By providing these critical services to the research community, NIAID can help to bridge gaps in the product development pipeline and lower the financial risks incurred by industry. For example, NIAID supports contracts to conduct *in vitro* screening of candidate drugs for HBV as well as hepatitis C virus; these contracts will be re-competed in FY 2011. In FY 2009, more than 800 compounds were screened for HBV antiviral activity.

Promising candidates can be further evaluated in appropriate animal models through contracts supported by NIAID. Through these contracts, candidate HBV drugs with novel mechanisms of action as well as new therapies to stimulate productive host responses to HBV infection are screened and evaluated with the goal of finding novel treatments that will work alone or in combination with current drugs to reduce or resolve chronic infections. Animal models supported by NIAID in FY 2010 include an HBV transgenic mouse model and a woodchuck infection model, which is considered the gold standard for preclinical HBV drug studies. These animal models are a critical tool to help identify new cellular and antiviral targets and develop new strategies for treatment of HBV infection.

#### Item

***Eosinophil-associated Disorders*** - The Committee urges the NIAID, in consultation with the NIDDK, NICHD, and NIMH, to convene a working group to develop a research agenda aimed at improving the diagnosis and treatment of eosinophil-associated diseases. The Committee requests an update on this effort in the fiscal year 2012 congressional budget justification. The Committee understands that a number of private sector organizations are interested in funding research in this area and encourages the NIAID to collaborate with these organizations as well as other NIH Institutes in supporting relevant research activities. (p. 104)

#### Action taken or to be taken

In certain diseases, including allergic diseases like asthma, eosinophils play a critical role. The proteins in eosinophils can damage the lungs and other organs and worsen inflammation at these sites. Eosinophilic gastrointestinal disorders (EGIDs) are a group of recently recognized allergic diseases associated with production of IgE antibodies and other immune responses to food. The most common EGID, eosinophilic esophagitis, is characterized by inflammation and accumulation of eosinophils in the esophagus. As the lead research institute at NIH that is responsible for immunologic and allergic disorders, NIAID works closely with other NIH Institutes and Centers supporting research on eosinophilic disorders. Although these collaborations and communications do not occur through a working group or a formalized research agenda, they are nevertheless effective and have led to jointly sponsored workshops and research initiatives on eosinophilic disorders.

NIAID is committed to research to understand the mechanisms that mediate tissue injury when eosinophils accumulate. In FY 2010, NIAID renewed the Consortium of Food Allergy Research (CoFAR), co-funded with NIDDK, to develop new approaches to treat and prevent food allergy. A new CoFAR project will examine the genetic aspects of eosinophilic esophagitis. The NIAID Asthma and Allergic Diseases Cooperative Research Centers, which will be re-competed in FY 2011, support basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases, including food allergy and anaphylaxis. Many of these disorders are associated with eosinophilia. Finally, on behalf of more than 30 professional organizations, Federal agencies, and patient advocacy groups, including the American Partnership for Eosinophilic Disorders, NIAID coordinated the development of

*Guidelines for the Diagnosis and Treatment of Food Allergy in the United States*, which will include clinical practice guidelines for the diagnosis and management of eosinophilic esophagitis associated with food allergy. The guidelines will be published in the December 2010 issue of the *Journal of Allergy and Clinical Immunology*.

NIAID researchers are conducting basic and clinical research on a variety of eosinophilic disorders. For example, researchers are following a cohort of more than 250 patients with eosinophilic disorders ranging from benign eosinophilia to eosinophilic leukemia. Clinical samples from the patients are collected for laboratory studies addressing the role of eosinophils in the various disorders. Investigators have identified a clinical subgroup of hypereosinophilic syndrome (HES) patients and begun study of treatments including imatinib and monoclonal anti-IL5 antibody therapy. Ongoing studies focus on identifying new markers to distinguish between HES variants, understanding eosinophil-associated pathology in HES, and using novel targeted therapies for HES. Other researchers are collaborating with colleagues from NIDDK to characterize immune cells in patients with EGID. The ultimate goal of these efforts is the development of new diagnostic tools and treatment approaches for eosinophilic disorders.

NIDDK supports a portfolio of basic, translational, and clinical research on the causes and treatment of EGIDs to improve fundamental understanding of these disorders and offer the possibility of improved therapy and diagnosis. For example, researchers are developing a patient registry to catalog clinical, pathologic, and translational outcomes for children with eosinophilic esophagitis, comparing the effectiveness of dietary modifications versus the use of steroid medications. In addition to supporting research studies, NIDDK provides funding to mentor young clinical investigators studying EGIDs. NIDDK has supported scientific conferences that assess the current state of basic and clinical research on EGIDs. In the future, NIDDK will continue to pursue the National Commission on Digestive Diseases' recommendations for research on EGID, which include studying its epidemiology and natural history; defining the genetic, cellular, and molecular mechanisms associated with disease; and identifying novel therapeutic compounds for treating this spectrum of disorders.

#### Item

**Inflammatory Bowel Disease (IBD)** - The Committee encourages the NIAID to expand support for IBD research through its Immune Tolerance Network and Autoimmune Disease Prevention Centers in collaboration with the IBD community. (p. 104)

#### Action taken or to be taken

NIAID continues its commitment to research toward better understanding the group of autoimmune diseases known as inflammatory bowel disease (IBD), a general term for a group of chronic, immune-mediated inflammatory diseases of the gastrointestinal tract, including Crohn's disease and ulcerative colitis. For example, the Institute supports research conducted through the Immune Tolerance Network (ITN) to evaluate novel, tolerance-inducing therapies in autoimmune diseases, such as IBD. The ITN is developing a study to assess the status of oral tolerance in patients with IBD. NIAID

also supports the Cooperative Study Group for Autoimmune Disease Prevention, which supported a pilot grant to define the effects of biological therapies on the immune systems of IBD patients.

The NIAID supports additional research programs focused on understanding what factors contribute to the development of autoimmune disease that may lead to improved understanding of the causes of these devastating diseases. For example, in FY 2010, NIAID renewed the Human Leukocyte Antigen Region Genomics in Immune-Mediated Diseases Consortium to define the association between a set of genes or genetic markers in the immune system and immune-mediated diseases, including one research project to study IBD. The NIAID is participating with other NIH Institutes in the NIH Human Microbiome Project, which is characterizing the microbiome associated with the human body and studying whether changes in the microbiome can be correlated with human disease. The project supports development of research resources for investigators, including a reference set of genomes from different body sites, new technologies, and new and improved bioinformatics tools. As part of the human microbiome project, researchers are studying human genes that are thought to confer a risk of IBD in order to determine whether these genes are associated with the development of necrotizing enterocolitis in premature infants. In addition, NIAID has recently released a request for applications, entitled Enterics Research Investigational Network (ERIN) Cooperative Research Centers (CRCs) that will establish a coordinated research program to bridge the gaps in basic, translational, and clinical research on enteric disease microbes. This initiative provides a funding opportunity for researchers studying IBD while also presenting opportunities for collaboration within the enteric diseases research community.

NIAID collaborates and coordinates with other NIH Institutes and Centers as well as other organizations with an interest in digestive diseases. NIAID also participates in the Digestive Diseases Interagency Coordinating Committee, which coordinates research on digestive diseases including the immunology, genetics, and role of the environment in IBD pathogenesis. NIAID participated in the National Commission on Digestive Diseases, which developed a long-range plan for digestive diseases research. NIAID is supporting several research programs that directly align with the goals of the National Commission on Digestive Diseases Report, including initiatives on mucosal immunology and microbial-host interactions, identification of genotypic variation with disease risk, characterization of the intestinal microbiome, and understanding basic mechanisms and infectious causes of IBD, which may yield insights into both adult and pediatric disease. In FY 2011, NIAID will launch the Immune Defense Mechanisms at the Mucosa program to support cooperative research projects on immune defense mechanisms and immune regulation at respiratory, gastrointestinal, and urogenital tract mucosal surfaces.

#### Item

***Microbicides*** - The recent results of the CAPRISA study in South Africa mark an important milestone for the field of HIV prevention. The Committee urges the NIH to continue to work with USAID, CDC, and other appropriate agencies to coordinate and

increase investment in microbicides research and development, prioritizing support for "next generation" ARV-based microbicides. The NIH is encouraged to support public-private partnerships that have a robust ARV product pipeline. (p. 104)

#### Action taken or to be taken

Encouraging results from a recent Centre for AIDS Programme of Research in South Africa (CAPRISA) microbicide trial (CAPRISA 004) demonstrated that a 1% tenofovir gel was 39% percent effective in preventing HIV infection. While data from this study are not definitive and results from additional trials are needed to confirm the findings, this study supports the concept that a microbicide could prevent HIV infection.

The NIH Office of AIDS Research (OAR) coordinates microbicide research activities across the NIH and the Federal government through a number of activities. OAR convenes the Trans-NIH Microbicide Coordinating Committee; experts from the Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration (FDA), and the U.S. Agency for International Development (USAID); and non-government experts from academia, industry, and the HIV community to develop the annual Trans-NIH Plan for HIV-Related Research, which includes the strategic plan for microbicide research and development and establishes trans-NIH research objectives and priorities. OAR also established and chairs a Trans-Governmental Microbicide Coordinating Committee, comprised of NIH institutes, CDC, FDA, the Department of Defense, the Department of Veterans Affairs, and USAID, to further facilitate coordination and collaboration in this area. In addition, the Microbicides Research Working Group (MRWG), an independent non-governmental panel of experts, advises NIH and other government and non-governmental entities that support microbicide research and development.

NIH, including NIAID, continues its strong support of research to identify and develop safe, effective, and acceptable microbicides through a highly collaborative program that provides support for basic research through preclinical development and clinical trials. For example, NIAID is working with CDC, the International Partnership for Microbicides (IPM), and CONRAD to coordinate a number of projects supported by NIAID's Integrated Preclinical-Clinical Program for HIV Topical Microbicides (IPCP-HTM) and Microbicide Innovation Program (MIP). These two programs support the development path of promising products to advance to clinical trials through the Microbicide Trials Network (MTN). The MTN, supported by NIAID, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the National Institute of Mental Health, collaborates with USAID, IPM, and CONRAD to test promising microbicides for safety and effectiveness.

Currently, through the MTN, NIAID is supporting the ongoing Vaginal and Oral Interventions to Control the Epidemic (VOICE) study. VOICE is a Phase IIb microbicide study examining daily use of tenofovir vaginal gel regardless of when women have sex to prevent HIV transmission. In addition, VOICE is testing daily use of oral ARV tablets, tenofovir alone, and tenofovir plus emtricitibine (Truvada®) for the ability to prevent the sexual transmission of HIV. The study is expected to enroll 4,200 women in Africa. The results of this study will build on the results of CAPRISA 004 to provide evidence to

support licensure of tenofovir gel and significantly extend the safety data available on tenofovir gel.

In addition, NIAID continues to collaborate with academia, industry, and foundations to identify and explore new and existing compounds that may warrant further study as potential microbicidal agents. For example, each of the five awards made under the Partnerships for Topical Microbicides program continue to make progress. The partnership awards join industry and academic or other non-profit organizations together in consortiums to develop and bring promising topical microbicide candidates to the point of preparation for clinical trials.

#### Item

***Neglected Tropical Diseases*** - The Committee is pleased that the NIH has included global health as one of its research priorities. The Committee encourages NIH to continue and expand its investment in neglected tropical disease, diarrheal, and arbovirus research and coordinate that work with other Government agencies to maximize resources and ensure development of basic discoveries into useable solutions. (p. 105)

#### Action taken or to be taken

Research focused on neglected tropical diseases (NTDs) has been part of the mission of NIH since its founding. NIAID has a long-standing program of research devoted to better understanding, treating, and preventing NTDs, which involves basic research on the biology of NTDs and pathogen-host interactions as well as translational research to facilitate development of new tools, interventions, and countermeasures against NTDs. The Institute partners with other U.S. government agencies, industry, and non-profit organizations in NTD research endeavors. NIAID also invests heavily in developing and strengthening sustainable local research capacity in NTD-endemic countries by providing scientists with access to critical research resources and training new investigators in the field.

In FY 2010, NIAID continued a broad malaria research program by supporting ten new International Centers of Excellence for Malaria Research awards. The goal of the Centers is to conduct multi-disciplinary research on malaria in all malaria-endemic regions of the globe. In FY 2009, NIAID made awards under the Development of Novel Interventions and Tools for the Control of Malaria, Neglected Tropical Diseases and their Vectors initiative. These awards stimulate early translational research leading to the development of novel therapeutic vaccines, diagnostics, and vector management strategies for malaria and NTDs. In FY 2010, NIAID also made new awards under the NIAID Partnerships with Product Development Public-Private Partnerships program. These awards are intended to facilitate later stage preclinical and translational research for NTDs, including Chagas' disease and human African trypanosomiasis.

NIAID researchers are studying NTDs such as lymphatic filariasis and leishmaniasis in U.S.-based laboratories and through NIAID's International Centers for Excellence in Research in India and Mali. This research, which is conducted in collaboration with

U.S., Indian and Malian government agencies, strives to improve the diagnosis and treatment of these diseases and to promote infrastructure development and research training. These efforts have resulted in widely used diagnostic tools for filariasis and leishmania infections.

NIAID scientists continue a longstanding research program in basic and applied arbovirus research with the development of a dengue vaccine that is now undergoing clinical trials in the United States. Additional candidate vaccines for dengue also are in various stages of development with support from NIAID.

NIAID will continue its support for the basic and translational research that is essential to better understand the biology and effective treatment of malaria and NTDs. The Institute remains committed to training local scientists and conducting and fostering research to develop new diagnostics, treatments, and vaccines. Partnerships between NIAID, other governmental and non-governmental organizations, and private industry will play a crucial role in building a solid product development pipeline to translate key basic science discoveries into needed, field-relevant tools.

#### Item

**Organ Donation** - The Committee recognizes the need for more intensive screening processes to prevent the transmission of viral, bacterial, and fungal infections from donors, and it urges additional research in this area in collaboration with the United Network for Organ Sharing. (p. 105)

#### Action taken or to be taken

Despite tremendous progress in organ and tissue transplantation, there are significant challenges to the long-term therapeutic success of an implanted organ or tissue. Barriers to short- and long-term success of transplant procedures are predominantly the result of incompatibility between donor and recipient, acute rejection, chronic allograft dysfunction, and complications of long-term pharmacologic immune suppression. NIAID's basic, translational, and clinical research programs in transplantation are committed to meeting these challenges and are working to improve long-term graft survival and to establish long-term tolerance without immunosuppressive drugs.

Disease transmission (infection or malignancy) from donated organs or tissues to transplant recipients, while uncommon, can have devastating consequences and affect numerous recipients of organs and tissues even if from a single donor. Results from NIAID-sponsored pediatric clinical trials in kidney transplantation provided critical support for the change in United Network for Organ Sharing policies on donor screening for Epstein-Barr virus. In addition, NIAID-sponsored clinical trials are addressing the harmonization of viral screening tests in organ donors and recipients and investigating the relationship between infection with common childhood viruses and the outcome of organ transplantation.

NIAID welcomes investigator-initiated applications to address disease transmission from donated organs or tissues to transplant recipients. NIAID programs in transplantation

include Clinical Trials in Organ Transplantation, Clinical Trials in Organ Transplantation in Children, the Immune Tolerance Network, and Immunobiology of Xenotransplantation Cooperative Research.

NIAID represents the NIH on the HHS Secretary's Advisory Committee on Organ Transplantation and the Scientific and Technical Advisory Committee and Post-Transplant Tumor Registry Technical Advisory Committee of the Scientific Registry of Transplant Recipients. NIAID will continue to participate actively in trans-HHS activities related to transplantation.

Item

***Tuberculosis (TB)*** - The Committee applauds the NIAID for its increased attention to the development of new TB diagnostics, drugs and vaccines, and it urges the Institute to continue to expand these efforts to halt the spread of TB, including drug-resistant TB. (p. 105)

Action taken or to be taken

NIAID remains committed to conducting and supporting research to gain in-depth knowledge about *Mycobacteria tuberculosis* (*Mtb*), the organism that causes tuberculosis (TB), and to translate this knowledge into improved interventions to prevent, diagnose, and treat TB. In addition to the conduct and support of research, the Institute is committed to providing comprehensive and integrated resources to facilitate the development of such interventions and translation into clinical practice. In 2008, as part of its program to address the emergence of drug resistance, NIAID developed the *NIAID Research Agenda for Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis (MDR/XDR-TB)* to identify current research and resource gaps in the study of drug-resistant TB and define priority research areas. The research agenda includes basic research as well as development of diagnostics, drugs, and vaccines.

NIAID supports research on new and improved diagnostics for TB and drug-resistant TB. For example, a TB diagnostic developed with NIAID support has shown exceptional promise in clinical trials, successfully identifying 98 percent of all confirmed TB cases and 98 percent of patients with rifampin-resistant bacteria in less than two hours. In addition, in FY 2009, NIAID funded the Clinical Diagnostics Research Consortium, which will evaluate early-stage diagnostic candidates in TB-endemic countries to facilitate selection of the most promising new tests.

The Institute also supports the development of novel therapeutics to combat TB and the emergence of drug-resistant TB strains. For example, SQ109, a drug developed with NIAID support, is being evaluated in a Phase 1b clinical trial in drug-sensitive *Mtb*-infected populations.

NIAID sponsors fundamental and clinical research leading to the development and testing of effective new vaccines for the prevention of TB, including a cooperative research grant for the *Development and Manufacture of Adjuvants for Vaccines Targeting MDR Tuberculosis*. Through the NIAID-supported Tuberculosis Research

Unit, researchers are conducting clinical trials of potential new TB therapeutic, preventive, and diagnostic strategies. Ongoing activities include the examination of TB vaccine efficacy in pediatric populations in South Africa.

NIAID has developed critical international collaborations to study the problem of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. For example, NIAID researchers and South Korean collaborators are conducting clinical studies at the Masan National Tuberculosis Hospital, which has the largest population of hospitalized MDR TB patients in the world. This collaboration has been expanded to include clinical studies of two drugs for the treatment of drug-resistant TB and crucial validation studies of the first rapid molecular test for XDR TB. In 2009, NIAID signed an Implementation Arrangement with the Henan Provincial Health Bureau to begin studies on highly drug-resistant TB in Henan province, China, which has the highest total number of reported cases of drug-resistant TB in the world. NIAID has provided support and training to scientists and physicians in the province to prepare for the studies. Under this agreement, a study to understand the correlates of a successful response to TB treatment began in July 2010.

NIAID continues to support investigator-initiated, basic research on TB to increase our fundamental knowledge of TB and *Mtb* pathogenesis. The development of improved vaccines, drugs, and diagnostics for TB, including drug-resistant TB, remains a high priority for NIAID.

#### Item

**Universal Flu Vaccine** - The Committee is encouraged that a universal influenza vaccine, which could potentially provide protection from all flu strains for decades, may become a reality because of research performed by the National Institute of Allergy and Infectious Diseases [NIAID]. Due to the strain-specific nature of current flu vaccine, the Committee recognizes that Federal funds could be saved every year and the public's health could be better protected if a universal influenza vaccine were available. The Committee encourages ASPR to work with NIAID to ensure that sufficient research is being done to develop and test a safe and effective influenza vaccine that protects against all strains of the virus. (p.177, 178)

#### Action taken or to be taken

NIAID conducts and supports a broad range of basic and translational research on influenza, including research and development of new therapies, diagnostics, and vaccines for both seasonal and pandemic influenza strains. Included in these efforts is research to develop a “universal” influenza vaccine that induces a potent immune response to the common elements of the influenza virus that undergo very few changes from season to season, and from strain to strain. A universal influenza vaccine has the potential to protect against multiple strains of the virus over several years.

Recent optimism for the development of a universal vaccine has come from work conducted by scientists at the NIAID Vaccine Research Center (VRC). The VRC is currently evaluating gene-based vectors in combination, and/or followed by standard

commercial seasonal influenza vaccine. The VRC researchers demonstrated that a two-step vaccination strategy—priming with a DNA-based vaccine followed by a boost with a vaccine similar to current influenza vaccines—was able to protect animals against multiple strains of influenza. Studies to assess the safety of this prime-boost influenza vaccine approach and its ability to generate immune responses are already under way in humans. The outcome of these trials can be valuable in selecting vaccine candidates to move forward into large-scale trials.

Additionally, NIAID supports a number of research projects to develop vaccines that induce an immune response to the common elements of the influenza A virus. Major targets in the search for a universal vaccine have been conserved regions from several different influenza proteins, including conserved internal proteins of the virus and conserved regions of the influenza envelope protein hemagglutinin that can serve as a common antigen for a vaccine. For example, NIAID-supported researchers recently generated a novel form of hemagglutinin without the variant portion. This conserved, “headless” hemagglutinin generated broadly cross-reactive antibodies against a number of divergent seasonal and pandemic influenza subtypes and provided protection against disease in mouse challenge studies.

NIAID also supports a wide range of resources to assist investigators in translating basic science into medical products such as improved influenza vaccines. These include *in vitro* assays, animal models, preclinical support as well as assistance with Phase I and Phase II clinical trials.

NIAID remains committed to supporting research that may lead to the development of a safe, effective universal influenza vaccine that could protect against multiple strains of influenza from season to season.

#### Item

***Vaccine Development for Hepatitis C*** - The Committee urges a refocused effort on the development of a hepatitis C vaccine and requests an update in the fiscal year 2012 congressional budget justification. (p. 105)

#### Action taken or to be taken

Hepatitis C virus (HCV) infection rates have steadily fallen in the last 20 years since the discovery of the virus and the development of detection tests, which have ensured the safety of blood transfusion products. Approximately 70 percent of HCV infections become chronic, often resulting in progressive and serious liver disease including cirrhosis and primary liver cancer. At present, treatment options are limited and on average, fewer than 50 percent of those treated are cured. Therefore, development of a safe, effective vaccine for HCV is a key step in working to prevent HCV infection and HCV-associated liver disease.

NIAID is committed to supporting research that will help advance understanding of hepatitis C virus biology and pathogenesis and contribute to the goal of a safe, effective

vaccine to prevent HCV infection. NIAID currently supports a variety of basic research and preclinical development activities to advance the development of an HCV vaccine.

In FY 2010, NIAID renewed support of the Hepatitis C Cooperative Research Centers, a network of five centers dedicated to defining successful immune response to HCV infection and identifying new targets for antiviral drugs, vaccines, and other therapeutic strategies for the prevention or treatment of acute and chronic HCV infection. Research conducted at the Centers will continue to advance understanding of the immune response to infection and the factors that determine the outcome of infection, either spontaneous or therapy-induced clearance or chronic persistence of HCV.

Currently, NIAID is in consultation with the U.S. Food and Drug Administration regarding the design of a Phase I/Phase II efficacy trial of a candidate HCV vaccine in intravenous drug users. This candidate vaccine was developed through a cooperative agreement supported by NIAID, and the trial is anticipated to begin in early 2011.

NIAID will continue pursuit of basic research and preclinical and clinical studies that will help to identify, develop, and test candidate HCV vaccines. The Institute will continue its support of studies to understand the immunological mechanisms that determine clearance or persistence of HCV in infected individuals. Finally, NIAID's collaborations with private and academic partners for preclinical development will help to advance development of candidate HCV vaccines.

## National Institute of General Medical Sciences (NIGMS)

### Senate Significant Items

#### Item

***Behavioral Research Training*** - The Committee applauds the Institute's leadership role in the OppNet initiative, which will support basic behavioral science throughout the NIH. The Committee encourages the NIGMS to support basic behavioral research to its fullest potential, and to incorporate basic behavioral training in its forthcoming training plan. (p. 105)

#### Action taken or to be taken

Launched in November 2009, the NIH Basic Behavioral and Social Sciences Opportunity Network (OppNet), a trans-NIH initiative to expand funding of basic behavioral and social sciences research, made awards totaling over \$10 million in fiscal year 2010. Supporting the growth of a cohort of scientists with research expertise in basic behavioral and social sciences through funding initiatives is also a major focus of OppNet. NIGMS is pleased to help lead this trans-NIH effort.

In addition to our role in OppNet, NIGMS continues to develop additional research areas in basic behavioral research, particularly focused on modeling approaches such as those used in the Models of Infectious Disease Agent Study (MIDAS) program. These involve collaborations between behavioral and social scientists with computer scientists to develop models that test our understanding of the impact of a range of social and other interventions on the behavior of populations. We have recently hired a program director in the Center for Bioinformatics and Computational Biology with strong interests in this area.

The NIGMS Strategic Plan on Training and Workforce Development is actively under development. This plan will cover strategies relevant to a broad range of training areas including training in basic behavioral research. NIGMS recently initiated a training program supporting research training at the behavioral-biomedical science interface. The strategic plan will focus primarily on cross-cutting issues of research training rather than specific training areas but will discuss training in emerging areas that lie at the interfaces of traditionally separate fields.

## National Institute of Child Health & Human Development (NICHD)

### Senate Significant Items

#### Item

***Adverse Pregnancy Outcome*** - The Committee is concerned that women with severe, early adverse pregnancy outcomes are at increased risk for long-term chronic health problems, including hypertension, stroke, diabetes, and obesity. The Committee urges the NICHD to undertake studies to identify women at risk for long-term morbidity and develop strategies to prevent long-term adverse outcomes in these women. (p.105)

#### Action taken or to be taken

NICHD has long embraced the concept that achieving healthy pregnancies will have beneficial long-term effects on the health of women and their families. NICHD has a long history of funding research to better understand the causes and development of severe, early adverse pregnancy outcomes such as preeclampsia, gestational diabetes, stillbirth, and preterm birth, as well as the management and prevention of these and other pregnancy conditions that may affect women's health over time.

NICHD funded the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) in January 2010 to study women whose current pregnancy will lead to their first delivery (nulliparas). NuMoM2b is a prospective cohort study of a racially, ethnically, and geographically diverse population of 10,000 nulliparas with single gestations that includes intensive research assessments during their pregnancies to study the prediction and prevention of adverse pregnancy outcomes. Nulliparas comprise about 40 percent of pregnant women in the U.S. and have been understudied to date. The collection of biospecimens and detailed clinical data will allow researchers to better understand the underlying mechanisms of, and predict the women at highest risk for, preterm birth, preeclampsia, and fetal growth restriction.

Maternal obesity, increasingly common in the U.S., is a major contributor to adverse pregnancy outcomes and long-term chronic health problems in women, such as hypertension, stroke, and diabetes. Excess weight gain during pregnancy can result in poorer birth outcomes, weight retention, and obesity after pregnancy. NICHD is funding an important clinical trial to test the effects of a pregnancy weight control program on improving maternal and infant outcomes in obese women, and a dietary intervention trial in obese pregnant women to reduce the risk of gestational diabetes and fetal macrosomia (i.e., babies who are born too large). Together with NHLBI, NICHD is supporting a trial using the internet and text messaging to promote healthy diet and physical activity during pregnancy in order to reduce the number of women who gain too much weight in pregnancy and who retain weight after delivery.

Women who develop diabetes during pregnancy (i.e., gestational diabetes) are at increased risk for developing type 2 diabetes in later years. The NICHD-supported Maternal Fetal Medicine Units Network recently reported results of a large clinical trial

showing that management of mild gestational diabetes during pregnancy reduces the number of babies who are born too large and other adverse outcomes. NICHD also is sponsoring an upcoming Consensus Development Conference on Gestational Diabetes.

Women with a history of preeclampsia have approximately double the risk of subsequent cardiac disease, peripheral arterial disease, and cardiovascular mortality compared to women without such history. Recently, NICHD cosponsored, along with NHLBI and other stakeholders, a workshop, “Bridging Preeclampsia and Future Cardiovascular Disease,” to examine the associations between preeclampsia and future cardiovascular disease. The primary goal of this meeting was to identify knowledge gaps and research opportunities in basic science and clinical practice.

#### Item

**Behavioral Neuroscience** - The Committee is pleased that the NICHD supports a broad spectrum of behavioral neuroscience research, particularly as it relates to real-world problems. The Committee encourages further work on the effects of socioeconomic adversity on children's brain development. (p.106)

#### Action taken or to be taken

NICHD has a long history of supporting research in behavioral neuroscience, including basic and applied studies of typical development, learning, and learning disabilities. This includes research on increasingly diverse populations, such as children living in poverty and minority children learning English as a second language. Recently, the Institute held three workshops addressing topics that encourage the integration of behavioral, genetic, and neuroimaging or neurobiological data: “Executive Function in Preschool Children,” “Cognition, Brain Function, and Learning in Incarcerated Youth,” and “Defining the Intersection of Reading and Math Disability Workshop.” All three workshops developed recommendations for next steps in research, including focusing on diverse groups of children and youth (e.g., children living in poverty, or facing developmental or physical disabilities, and members of understudied and underserved minority groups), increasing the use of modern neuroimaging techniques, and new markers of brain activity.

NICHD contributed to the trans-NIH Pediatric Study of Normal Brain Development, which developed a large, longitudinal database of structural brain images of children from birth through age 22 years. That database is now available and is being used widely by researchers around the world. As a follow-up to this effort, NICHD is working with the Children’s Hospital of Cincinnati to develop software and brain activation tasks for directly assessing brain blood flow in typically developing infants, children, and adolescents. The blood flow data will be coordinated with functional magnetic resonance imaging (MRI) data, and the result will be a database of approximately 300 typically developing children. This project will enhance our knowledge of typical brain development and offer a comparison group for researchers studying diverse samples of children with a variety of conditions.

NICHD also supports a research network of cooperative agreement grants (with collaboration with Administration for Children and Families) that is testing interventions in young children learning English, and a centers program on learning disabilities. The Learning Disabilities Research Centers consortium currently includes four geographically distributed centers (in Colorado, Florida, Texas, and Maryland) that are addressing the behavior, neurobiology, and genetics of reading and reading disabilities. The centers program was recompeteted in 2010. Applications received in response to two recently issued solicitations, “Learning Disabilities Research Centers” and “Learning Disabilities Innovation Hubs,” will be reviewed for funding in late fiscal year 2011. In addition to supporting four or five centers, NICHD plans to expand the program to support smaller center-like grants aimed at developing innovative approaches to remediating learning disabilities (both reading and math) and supporting early stage investigators to build research capacity in learning disabilities.

#### Item

***Chromosome Abnormalities*** - The Committee again urges the NIH to convene a state of the science meeting on chromosome abnormalities involving multiple contiguous genes in order to create a plan to collect data regarding dosage-sensitive and dosage-insensitive genes and establish phenotyping and genotyping standards for data collection. The Committee also encourages the NIH to provide new funding to support independent investigators whose work can provide pilot data or insight into future directions for the study of chromosome abnormalities, particularly those involving chromosome 18. (p.106)

#### Action taken or to be taken

The advent of new technologies (e.g., cytogenomic arrays) has facilitated identification of chromosome differences in children with otherwise unexplained developmental delay, intellectual disability, autism, or multiple birth defects. Research in this field is focused on the identification of critical genes within copy-number variations (CNVs). The number of copies of a particular gene in an individual’s genome, accounts for a significant proportion of the genetic variation among individuals. In support of a coordinated effort to catalogue these CNVs for clinical use and research purposes, the NICHD and the NIH Office of the Director are funding a Grand Opportunity (“GO”) grant with American Recovery and Reinvestment Act funds to develop a comprehensive atlas of CNVs. The atlas will include a large amount of standardized clinical data collected from pediatric and prenatal populations and deposited into an NIH-supported central public data repository. The International Standards for Cytogenomic Arrays Consortium held a workshop in June 2010 to develop standards for evaluation and interpretation of cytogenomic arrays, to discuss standardizing the design and data format, and to plan for implementing and disseminating the CNV atlas. A public conference also is being planned for late January 2011 with support from the GO grant. With more than 160 member laboratories and 15,000 arrays collected thus far, the consortium is poised to establish high-quality standards for genotyping and phenotyping of chromosome abnormalities that involve multiple contiguous genes and may ultimately affect the clinical care and reproductive risks for families with an identified CNV.

The NICHD currently supports grants that address a number of disorders caused by deletions or duplications of chromosomal material that include multiple contiguous genes, although no currently funded grants focus solely on chromosome 18 disorders. Down syndrome is one example of such a disorder, caused by the presence of an extra copy of chromosome 21. The triplication of a subset of genes on chromosome 21 (the Down syndrome “critical region”) is likely to result in particular physical and cognitive effects. Research progress on Down syndrome is progressing on a number of fronts, including several upcoming Program Announcements, and planning for an upcoming meeting to discuss a contact registry, research database, and biobank. The NICHD portfolio also includes investigator-initiated grants that cover a spectrum of contiguous gene disorders, such as Williams’s syndrome, Smith-Magenis syndrome, Potocki-Lupski syndrome, DiGeorge (or Velocardiofacial) syndrome, Angelman syndrome, and Prader-Willi syndrome. An NICHD funded Rare Disease Clinical Research Consortium for Rare Epigenetic Disorders also supports research on Angelman, Rett, and Prader-Willi syndromes. Among its activities, the Consortium focuses on natural history studies; the use of cytogenomic arrays to determine the extent of deletions in patients with Prader-Willi syndrome-like features, or in those with early morbid obesity; and the development of new diagnostics and therapies for these conditions. The NICHD also funds studies of critical genes on the X chromosome that may play a role in the clinical features of Turner syndrome, one of the most common chromosomal disorders in females, caused by absence of X chromosome material.

#### Item

***Contraceptive Research and Development*** - The Committee encourages the NICHD to strengthen its support for contraceptive research and development for the prevention of unintended pregnancies and the efficacy and safety of hormonal contraceptives among overweight and obese women. The Committee additionally urges the Institute to identify opportunities and research priorities in contraceptive development, such as the need for non-hormonal contraception, post-coital contraception and multipurpose technologies that would prevent both pregnancy and sexually transmitted infections. (p.106)

#### Action taken or to be taken

Because of the accompanying increased risk of venous thromboembolism, hormonal contraceptive use by overweight and obese women has raised health concerns. In addition, it is unclear whether hormonal contraception may be less efficacious when used by obese women. While alternative nonhormonal methods of contraception exist for these women, hormonal oral contraception is the most commonly used and acceptable of the current methods available in the U.S. To identify the gaps in knowledge and research around this topic, NICHD convened a workshop of international experts on hormonal contraception, obesity, and risk of venous thromboembolism in late 2010. A summary of the meeting, including potential avenues for future research, is available.

Through its Contraception and Reproductive Health Branch, NICHD is actively involved at all stages in the development of new contraceptives, from basic research to Phase III

clinical trials and preparation for FDA approval. NICHD is supporting the development of both male and female nonhormonal contraceptives through four Contraceptive Development Research Centers and in eight sites of the Male Contraceptive Development Program. While the Contraceptive Development program is primarily supporting basic research, a concerted effort has been made to encourage the investigators to focus on specific drug targets with the goal of developing acceptable and effective contraceptive products for men. In August 2010, the FDA approved for marketing in the U.S. a postcoital contraceptive developed with NICHD support. Through a licensing arrangement with a pharmaceutical firm, the product is currently being marketed in Europe and was made available in the U.S. in early 2011.

In addition, NICHD has been actively funding research on multipurpose technologies, including vaginal microbicides. For example, a Phase III contraceptive efficacy trial of a new female condom that would be effective for the prevention of both pregnancy and sexually transmitted infections began in FY 2010. This new female condom has a novel design and is likely to have a much higher level of acceptability than previous female condoms.

#### Item

**Demographic Research** - The NICHD's historic support for demographic research on the non-aged population has yielded landmark scientific findings, confirming how health and well being in the early years affects long-term health and socioeconomic outcomes. Many of these advances have derived from the Institute's investment in large-scale, longitudinal studies, such as the National Longitudinal Study of Adolescent Health and Child Development Supplement to the Panel Study of Income Dynamics, and inter-agency studies, including the National Survey of Family Growth and National Longitudinal Survey of Youth. The Committee expects the Institute to sustain its support for these important resources and reaffirm its commitment to supporting research on how maternal factors before and during pregnancy and early life events affect health and well being in later life. (p.106)

#### Action taken or to be taken

NICHD has continued its support of large-scale, nationally representative, longitudinal data sets such as the National Longitudinal Study of Adolescent Health (Add Health) and the Child Development Supplement (CDS). Add Health follows the developmental and health trajectories of a sample of children in the U.S. first interviewed in grades 7-12 during the 1994-95 school year, and most recently interviewed at ages 24-32 in 2008-09. The CDS has followed a sample of children since they were between 0 and 12 years old in 1997, providing detailed data on the processes by which families support themselves financially through economic cycles. In 2010, CDS researchers have published findings on topics such as neighborhood influences on high school graduation rates over time, the long-term impact of Head Start programs on smoking behavior, and the long-term effects of psychological problems during childhood.

Other valuable data sets supported by NICHD include the New Immigrant Study, which is providing the first representative longitudinal data on legal immigrants to the U.S. and

their families, and the Work, Family, and Health Network, which is currently examining how a workplace intervention may benefit workers, their spouses and children, and provide overall benefits for the employers' businesses. NICHD also supports research on various external factors experienced by women during pregnancy, such as low socio-economic levels, and how those factors may influence health outcomes for both them and their children. The NICHD-funded Fragile Families and Child Well-Being Study focuses on children born to unmarried parents to assess how financial resources, father involvement, and parenting practices affect children's health and development.

NICHD also continued its interagency agreement with the CDC to support the National Survey of Family Growth (NSFG). The NSFG gathers information on family life, marriage and divorce, pregnancy, infertility, use of contraception, and women's and men's health. The survey results are used by the Department of Health and Human Services and other federal agencies to plan health services and health education programs, and by the research community to conduct statistical studies of families, fertility, and health. Research based on these data over the past year has shed light on how food prices influence fruit and vegetable consumption among young adults and the dynamics of obesity and chronic health conditions among children and youth.

NICHD plans to continue its support for these and other important demographic studies.

#### Item

**Fragile X Syndrome** - The Committee encourages the NIH to implement the NIH Research Plan on Fragile X Syndrome and Associated Disorders and continue to fund translational research that shows significant promise of a safe and effective treatment for Fragile X-associated Disorders [FXD]. (p.106)

#### Action taken or to be taken

The NIH Fragile X Research Coordinating Group (FXRCG) continues to meet twice yearly to discuss current research in fragile X syndrome and the associated disorders of fragile X-associated tremor/ataxia (FXTAS) and fragile X-associated primary ovarian insufficiency (FXPOI). The group annually reviews the array of research related to the NIH Fragile X Research Plan to identify possible opportunities for collaboration, gaps in the research, and potential ways to address those gaps. Members of other Federal agencies (Centers for Disease Control and Prevention, Health Resources and Services Administration, Department of Defense) with a stake in fragile X research, also participate in the FXRCG to coordinate research goals across the government. In addition, NICHD regularly participates in the meetings of the Fragile X Clinical & Research Consortium and the annual National Fragile X Conferences.

NICHD continues its commitment to research on the early identification of children with fragile X syndrome and to gain a better understanding of the special challenges faced by their families. Through the Fragile X Research Centers, NICHD supports a variety of projects addressing these issues, including studies that evaluate maternal responsivity and development of children with fragile X syndrome, the adaptations of families of adolescents and adults with the condition, and family adaptation to a diagnosis of fragile

X syndrome through newborn screening. The Fragile X Research Centers conduct research aimed at clarifying the developmental consequences of the full spectrum of the fragile X syndrome in infants. NICHD also supports research projects to develop novel, cost-effective diagnostics for fragile X syndrome and a research consortium that focuses on intervention strategies for FXTAS. The projects range from an effort to identify small molecules as potential lead compounds for potential therapeutics, to a study on the use of a metabotropic glutamate receptor antagonist for treating fragile X syndrome. An additional study funded by NINDS also focuses on the development of a potential treatment to suppress neurodegeneration in FXTAS.

In FY 2010, NICHD published a program announcement to solicit grants that will develop beneficial treatments for infants identified through newborn screening, including babies with fragile X syndrome.

#### Item

***Intellectual and Developmental Disabilities Research Centers (IDDRCs)*** - The Committee continues to recognize the outstanding contributions of the IDDRCs toward understanding the causes for a wide range of developmental disabilities including autism, Fragile X syndrome, Down syndrome and other genetic and environmentally induced disorders. The Committee is particularly pleased with how the IDDRCs have collaborated with each other to leverage resources and scientific capital on such efforts as developing a pilot national registry of patient populations and training and supporting young scientists. These centers received administrative supplements through the American Recovery and Reinvestment Act of 2009 that were used to purchase equipment and develop enhanced scientific core services. However, the Committee urges the NICHD to provide additional resources to the IDDRC network to help bring about progress in expanding registries to include larger samples across different disorders, support and mentor new investigators, and develop opportunities for translational research efforts. (p.106,107)

#### Action taken or to be taken

The *Eunice Kennedy Shriver* Intellectual and Developmental Disabilities Research Centers (IDDRC) program provides support for research infrastructure for independently-funded projects whose goals are to understand the causes of intellectual and developmental disabilities (IDD) and to develop treatments for these disorders. In recent years, NICHD has funded 14 IDDRCs, providing five-year grants to universities and children's hospitals throughout the country; these grants are recompeteted on a rolling basis. The most recent competition added a fifteenth IDDRC that will focus on cerebral connectivity, genetics and environmental influences on brain development, and efforts to prevent and treat conditions ranging from brain injury in premature infants to autism spectrum disorders. Three other IDDRCs successfully recompeteted this past year and will continue their strong research programs in genetic/genomic disorders, inborn errors of metabolism, and mitochondrial disorders.

NICHD awarded almost \$2 million dollars in American Recovery and Reinvestment Act funding to 13 IDDRCs. Among the projects funded is the creation of a shared contact registry of individuals with Fragile X syndrome that will become an IDDRC resource to

support investigators interested in studies involving this condition, and serve as a potential model for registries for other forms of IDD. In addition, nearly one million dollars in supplements was awarded in FY 2010 to support the three Fragile X “Centers within Centers,” housed within the structure of the existing IDDRCs to support basic molecular studies of the pathogenesis of Fragile X syndrome, the development of animal models of the condition, and translational studies on the impact of diagnosis through newborn screening on families.

IDDRCs also encourage the development of new investigators in IDD research. Amended IDDRC program guidelines now allow expanded access to IDDRC “cores” (i.e., equipment, services and technical support) for these young investigators, even if they lack their own NIH funding. A new NICHD-supported conference grant funded the first Interdisciplinary Training Conference in Developmental Disabilities in March 2010, a one-day workshop to promote mentoring and career development, bringing together many NICHD staff with junior and senior investigators in the field. This workshop accompanied the annual Gatlinburg Conference on Research and Theory in Intellectual and Developmental Disabilities.

#### Item

***Maternal Fetal Medicine Units Network*** - The Committee continues to encourage the NICHD to support this network. (p.107)

#### Action taken or to be taken

The Maternal Fetal Medicine Units Network (MFMU) supports 14 clinical sites across the United States through cooperative agreements. This network is openly and actively recomputed every five years. NICHD supports a base infrastructure to allow for continuity and as a platform for the clinical trials, allowing for significant cost savings, since multiple trials can be ongoing at once. NICHD has partnered successfully with other NIH Institutes to support clinical trials conducted through the network. For example, NHLBI supports a trial evaluating whether antenatal corticosteroids administered during the 34-37<sup>th</sup> week of pregnancy will improve health outcomes for infants. NINDS is supporting a followup study of five-year old children enrolled in a study to look at the effects of subclinical hypothyroidism or hypothyroxinemia to look at the effects on child IQ.

The MFMU network has had remarkable success in completing high quality trials that are published in top tier journals and whose findings are incorporated into practice through dissemination by professional organizations such as the American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine. One new intervention, which was shown to reduce the rate of cerebral palsy in the offspring, is treatment with magnesium sulfate during pregnancy for women at high risk of preterm birth. Cerebral palsy refers to a group of neurological disorders affecting movement and posture, and which can severely limit physical activity. In this study, one case of cerebral palsy was prevented for every 63 women at risk of preterm birth who were treated. The network also provided the data that treatment of even the mildest form of gestational diabetes improves maternal and neonatal outcomes, with significant

reductions in large babies, shoulder dystocia (difficult delivery due to the baby's shoulder getting stuck during delivery), cesarean delivery, gestational hypertension, and preeclampsia. A recent study indicated that only 12 to 40 women need to be treated for gestational diabetes to prevent one of these outcomes.

The MFMU network also has identified new interventions and practices that confer no health benefits and may actually cause harm. Among the many examples of MFMU trials that stopped unnecessary practices was one on fetal pulse oximetry; it found that using pulse oximetry as an adjunct to fetal heart rate monitoring in labor did not reduce cesarean deliveries or improve neonatal outcomes. Similarly, routine screening and treatment for bacterial vaginosis in pregnant women was shown to slightly increase the preterm birth rate, instead of reducing it.

The MFMU network is a leader in providing the evidence for obstetrical and maternal fetal practice. These data are also used to develop consensus conferences on topics of public health importance. Network data was extensively used in the Vaginal Birth After Delivery (VBAC) Consensus Conference held in early 2010, and is the basis for an upcoming consensus conference on gestational diabetes.

#### Item

***Metabolic Disease and Bone Health*** - The Committee urges more research in the emerging field of metabolic disease and bone health in children and adolescents, especially childhood obesity, anorexia nervosa, and other eating disorders. Research is also needed on what the optimal vitamin D levels should be in children to achieve maximal bone health and the implications of chronic seasonal vitamin D deficiency to the growing skeleton. Development and testing of therapies and bone-building drugs for pediatric patients are also a pressing clinical need. (p. 107)

#### Action taken or to be taken

The NICHD-supported Bone Mineral Density in Childhood Study (BMDCS) has provided more information on bone growth and sexual development in childhood than any other single study to date. In the past six years of data collection, this study has established the effects of pubertal timing, body mass index (BMI), nutrition, and exercise on bone mineral accretion. A unique follow-up study, currently in the planning phase, could answer important questions about the long-term effects of nutrition, adiposity, and pubertal timing on bone mineral accrual and peak bone mass. In the future, these data could enable researchers to test therapies and bone building drugs in pediatric patients with low bone mineral density (BMD) or inadequate bone accrual.

Patterns of bone mineral accretion in childhood during the various stages of growth and sexual maturation suggest a heritable component separate from body size. To understand this process and to identify genetic variants associated with BMD and bone mineral accretion, BMDCS investigators have initiated genome wide association studies (GWAS) of this carefully documented cohort.

NICHD-funded researchers also are focusing on the effects of nutritional deprivation and chronic stress on bone accrual and fracture risk, specifically among adolescents with anorexia nervosa. Findings indicate that variables in bone strength in this population may have implications for fracture risk. Using magnetic resonance imaging, the work suggests that the early osteoporosis and increased fracture risk in this group may stem from early changes in bone marrow due to their condition.

Researchers supported by NICHD recently conducted a longitudinal study to determine the seasonal variation of vitamin D status in adolescent African Americans and Caucasian children. They concluded that season, not skin color, was a determinant of vitamin D status. These researchers now are conducting a longitudinal randomized trial of daily vitamin D versus a placebo in 8 to 14 year-old children to examine vitamin D deficiency prevention and bone health. Markers of bone turnover, vitamin D status, diet, and sun exposure will be monitored.

A number of genetic determinants of adult BMI have already been robustly established through GWAS. NICHD-funded investigators showed that the same genetic variant that is strongly associated with Type 2 Diabetes (T2D) in adults also influences pediatric BMI, thus demonstrating its possible mode of action in conferring the risk for the disease in later life. In a recent GWAS study of birth weight, several genes were implicated in regulation of glucose levels and susceptibility to T2D, providing evidence that the association between lower birth weight and subsequent T2D has a genetic component.

#### Item

***Pediatric Research Acceleration*** - The Committee recognizes that the NIH and the NICHD in particular use a variety of mechanisms to support pediatric research, including condition-specific centers, clinical trials networks, and the Clinical and Translational Science Awards. The Committee nevertheless remains concerned as to the overall level of support for pediatric biomedical research, particularly for initiatives that focus on the continuum from basic to translational research; that provide infrastructure support, particularly to early-career researchers; and that are connected through a networked approach that encourages resource sharing and collaboration. The Committee urges the NIH to support a networked pediatric research consortia model and requests an update on this request in the fiscal year 2012 congressional budget justification. (p.107)

#### Action taken or to be taken

In FY 2009, NIH, through 22 Institutes and Centers (ICs), awarded approximately \$3.2 billion in support of pediatric research activities across the country. The funding was distributed to the research community through the full range of available funding mechanisms, including investigator-initiated grants, contracts, and research networks. This flexibility allows the extensive scientific expertise at NIH and across the extramural scientific research community to judge which mechanism(s) might be best suited for the specific research needed to answer questions about children's health and development, diseases and conditions. Less commonly, but where the scientific challenge warrants

and funding permits, NIH ICs (often in trans-institute collaboration) have created multidisciplinary centers of excellence or research networks for specific pediatric populations or conditions, such as autism, pediatric oncology, neonatology, and adolescents with HIV/AIDS, to name a few.

A number of the Clinical and Translational Science Awards (CTSAs) sites include a strong emphasis on creating a national infrastructure to conduct pediatric clinical trials, allowing pediatric researchers who focus on a wide variety of conditions to utilize this new resource and to conduct clinical trials efficiently and effectively. CTSAs and their pediatric components provide a rare opportunity for researchers from across the country to combine multi-disciplinary and community-based resources to implement standard approaches for addressing the unique challenges in child health research.

In evaluating the appropriate mechanism or infrastructure to use to address any question about health or disease, important considerations must include whether the proposed mechanism provides the range of scientific expertise required to answer that question, the availability of a sufficiently sized study population, and whether a currently existing mechanism might adequately meet these needs. The impact of creating a new infrastructure on investigator-initiated proposals also must be weighed. NICHD is continuously looking for ways to increase collaboration and cooperation among researchers. The “hub and spoke” model is certainly one approach, and the Institute plans to review existing networks of pediatric researchers to see whether this approach might best serve the needs of the pediatric research community and the children who may benefit from the research.

#### Item

***Preterm Birth and Stillbirth*** - The Committee urges the NICHD to expand its support of preterm birth related research by exploring the feasibility of establishing integrated transdisciplinary research centers as recommended by the Institute of Medicine and the Surgeon General's Conference on the Prevention of Preterm Birth. NICHD is also encouraged to take advantage of high throughput technologies to understand the causes of preterm birth and stillbirth, and to support genomics, proteomics, and metabolomics studies focusing on prediction and prevention of preterm birth and stillbirth, as well as the use of existing biobanks. (p.107)

#### Action taken or to be taken

NICHD appreciates the value of integrated transdisciplinary research centers and is funding two such networks related to preterm birth. The Genomics and Proteomics Network for Preterm Birth Research (GPN-PBR) consist of three core functions. Three sites provide clinical expertise and are responsible for subject recruitment and specimen collection. One site provides the analytical expertise necessary for high-throughput genomic and proteomic analyses. Another site, for Data Management, Statistics, and Informatics, provides essential sophisticated bioinformatics expertise. Another center within the network is a program project grant, Overall-Gene-Environment Interactions in Human Parturition. Several years ago, NICHD recognized the need for a biobank suitable for use by the preterm birth research community. The large collection of

biological specimens collected by the GPN-PBR will be deposited in a NICHD repository and access to these specimens will be made publically available sometime in 2011-2012.

NICHD funded the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) in January 2010 to study women whose current pregnancy will lead to their first delivery (nulliparas). NuMoM2b is a prospective cohort study of a racially, ethnically, and geographically diverse population of 10,000 nulliparas with single gestations that includes intensive research assessments during the pregnancies to study the prediction and prevention of adverse pregnancy outcomes. Nulliparas comprise about 40 percent of pregnant women in the U.S., and have been understudied to date. The collection of biospecimens and detailed clinical data will allow researchers to better understand the underlying mechanisms, and predict the women at highest risk for preterm birth, preeclampsia, and fetal growth restriction.

In 2003, NICHD established the Stillbirth Collaborative Research Network (SCRN) to understand the epidemiology and causes of stillbirth (defined as fetal death at 20 weeks' gestation or greater), which accounts for half of perinatal mortality. The objectives of the initiative are to: 1) develop a standard stillbirth postmortem protocol that includes a review of clinical history, protocols for autopsies, and pathologic examinations of the fetus and placenta; 2) develop other postmortem tests to illuminate possible genetic, maternal, and other environmental influences on stillbirth; and, 3) to obtain a geographic, population-based determination of the incidence of stillbirth, its causes, and risk factors. SCRN has completed recruitment for a prospective, multicenter, population-based, case-control study of all stillbirths occurring in 59 hospitals across the U.S. High-throughput technologies are now being applied to uncover genetic and infectious causes of stillbirth that are not diagnosed by conventional methods. For example, genomic technologies are being used by the SCRN to look at the copy number changes that may cause stillbirth, and to investigate the microbiome. The results of these analyses will be available in 2011.

#### Item

***Psychosocial Stress in Children*** - The NICHD is encouraged to develop a program of research to better understand the immediate and long-term effects of stress in children, in contexts including families of deployed military personnel, and experiences in natural disasters and war zones. (p.107)

#### Action taken or to be taken

Emergencies and disasters include severe weather-related events, earthquakes, and large-scale attacks on civilian populations, technological catastrophes, and influenza pandemics. In recent years, NICHD has funded several major studies focused on disaster-related research, including adversity and resilience after Hurricane Katrina; the social and economic effects of natural disasters; and marriage, birth, and divorce after terrorist attacks. For example, a study supported by NICHD entitled, "Violence and Mental Health: Children of First Responders," addresses children's experiences when their parents respond to natural disasters and war. In FY 2010, NICHD joined in a

Funding Opportunity Announcement with three other NIH institutes to call for expanded behavioral and social research on disasters and health. The purpose of this announcement was to stimulate research in the behavioral and social sciences on the consequences of natural and man-made disasters for the health of children, the elderly, and vulnerable groups, with an ultimate goal of preventing and mitigating harmful consequences and health disparities.

Multiple deployments and reintegration of military personnel can have a significant impact on children living in military families. NICHD funds three investigator-initiated studies on this topic and continues to encourage related research and conference support in this area. One study, unique in its focus on children's behavior and emotional functioning, showed that a parent's combat deployment has an adverse effect on children that increases the longer the parent is away; these effects remained even after the parent returned home. An ongoing grant is evaluating a community-based, longitudinal intervention of a marriage education program delivered by Army Chaplains for Army couples. This new program, Prevention and Relationship Enhancement Program (PREP), is specifically adapted for young Army couples from an existing evidence-based intervention targeting risk and protective factors for marital conflict and distress, particularly those factors that have been shown to be strongly associated with a range of individual and family problems.

A Small Business Innovation Research Grant also is targeting innovative ways to strengthen family functioning and improve child outcomes in military families after deployment. The grant will allow a small business in partnership with several academic institutions and Federal agencies, to develop, evaluate, and disseminate tools to assist in post-deployment parenting. These tools will provide an online, interactive resource for military parents, targeting veteran families who are at risk for depression, anxiety, substance abuse, mental illness, and post-traumatic stress, among other conditions.

The Department of Defense's Centers of Excellence jointly held three major national scientific meetings, most recently in December 2010, to understand the impact of Post Traumatic Stress Syndrome (PTSD) and Traumatic Brain Injury (TBI) on military service personnel and veterans. NICHD has played a lead role in organizing sessions focusing on the impact of combat related-stress and military deployment on child and family functioning with a particular focus on how parental military deployment, service, and reintegration affect overall family adjustment.

#### Item

**Vulvodynia** - The Committee is encouraged by positive signs that the NICHD is devoting greater attention to this long-neglected condition, especially with regard to stimulating interest in the research community and ensuring adequate representation of vulvodynia experts on peer-review panels. The Committee expects to be updated on progress in these areas. The Committee also notes that vulvodynia coexists with other persistent pain conditions, including interstitial cystitis, fibromyalgia, temporomandibular joint and muscles disorders, irritable bowel syndrome, endometriosis, headache and chronic fatigue syndrome. The Committee strongly urges the creation of a trans-NIH

research initiative that will support studies aimed at identifying common etiological pathways among these disorders, with the goal of developing potential therapeutic targets. (p.107, 108)

#### Action Taken or to be Taken

Vulvodynia remains one of the poorly understood complex chronic pain syndromes, representing a multifactorial clinical syndrome of unexplained sexual dysfunction and chronic vulvar irritation, burning, and pain. Some published studies suggest that central and peripheral neurological processes may contribute to vulvodynia pain symptoms in many women. NICHD agrees that research focused on identifying common etiological pathways among vulvodynia, other coexisting pain disorders, and co-morbid conditions, would greatly increase understanding of pain syndromes and facilitate future development of therapeutic options.

Recognizing that this is an important area of research, NICHD has issued six previous Funding Opportunity Announcements (FOAs) on vulvodynia, outlining a scientific framework for potential applicants. Despite these efforts, only limited numbers of grant applications were submitted. To address this issue and expand research capacity in this area, NICHD is using a coordinated approach to the application and review process afforded through a Program Announcement with Referral and Special Review (PAR). NICHD recently published three new FOAs, using the Research Project, Small Research Grant, and Exploratory/Developmental Grant award mechanisms, specifically targeted toward vulvodynia. Applications in response to the three FOAs may be submitted through 2012. These initiatives, cosponsored by the NIH Office of Research on Women's Health, should increase understanding of the pathophysiology, mechanisms of pain development, epidemiology, environmental and genetic influences, and clinical therapeutics related to vulvodynia. To provide technical assistance to prospective applicants planning to submit applications, NICHD convened a preapplication workshop in August 2010. Information presented at the meeting also is available on the NICHD website.

In addition, NICHD is planning to convene a conference on vulvodynia and related chronic pain syndromes in the summer of 2011. The planning committee will consist of representatives from relevant NIH Institutes and Centers, investigators from the vulvodynia and chronic pain research communities, and public representatives. The purpose of the meeting is to identify promising research avenues that will continue to build upon and enhance our understanding of the basic research conducted to date, and create a trans-NIH plan for pursuing that research.

## National Eye Institute (NEI)

### Senate Significant Items

#### Item

**Cataracts** - The Committee is encouraged by the NEI's collaboration with NASA in developing a new diagnostic technology that identifies those at risk for cataract development before it is clinically detectable. (p.108)

#### Action taken or to be taken

Dynamic Light Scattering (DLS), the first diagnostic technology developed to detect early stages of cataract, may become a standard tool in ophthalmic care. The DLS technique now will assist vision scientists in looking at long-term lens changes due to aging, smoking, diabetes, LASIK surgery; eye drops for treating glaucoma, and surgical removal of the vitreous gel within the eye, a procedure known to cause cataracts within six months to one year. It also may help in the early diagnosis of Alzheimer's disease, in which an abnormal protein may be found in the lens. In addition, the ability to detect pre-cataractous lens protein changes also will enable investigators to evaluate drugs that potentially prevent cataract formation. Moreover, NASA researchers will continue to use the device to look at the impact of long-term space travel on the visual system.

#### Item

**Leber Congenital Amaurosis** - The Committee is encouraged by recent reports of initial success in treating Leber congenital amaurosis with gene therapy and is pleased that the NEI will evaluate gene transfer in younger patients with less severe disease. The Committee urges the Institute to pursue studies of this promising treatment on an expedited basis in other genetically inherited, retinal degenerative diseases. The Committee requests an update on such efforts in the fiscal year 2012 congressional budget justification. (p.108)

#### Action taken or to be taken

In 2007, the National Eye Institute launched a phase I clinical trial to assess the safety of gene transfer in humans with a form of Leber congenital amaurosis (LCA). This is the first clinical trial to assess gene therapy in humans with eye disease. People with LCA are born with severe visual impairment or lose their vision in early childhood. The form of LCA being evaluated in this study results from mutations in the RPE65 gene which plays a critical role in the visual cycle, the set of biochemical reactions that convert light into an electrical signal to initiate vision. Mutations in the RPE65 gene disrupt the visual cycle resulting in LCA. Fortunately, the structure of the retina remains relatively intact into early adulthood, providing an opportunity to intervene therapeutically.

In 2009, investigators published one year follow-up results of the three patients who received this investigational therapy. The patients, ranging in ages from 22-25,

remained healthy and experienced no adverse events. Statistically significant increases in light sensitivity were found in the first three months of the trial in all patients and remained unchanged at one year. Rigorous clinical examinations corroborated that the visual improvements were found in the treated area of the retina, lending further objective evidence of the treatment's efficacy. These data also correlate with subjective reports by patients of improved vision. This landmark clinical trial will next evaluate gene transfer in younger patients with less severe disease, which may prove more efficacious.

Gene transfer is particularly well-suited to the treatment of retinal degenerative diseases. Nearly 200 single gene defects have been implicated in these diseases. NEI remains enthusiastic that gene therapy could one day become an invaluable treatment for a variety of eye diseases. Recently published laboratory studies targeting optic atrophy, color blindness, and several rare retinal diseases have demonstrated proof-of-concept that gene transfer offers therapeutic benefit. Positive findings in these studies now allow investigators to expedite the pre-clinical work necessary to pursue regulatory approval to conduct clinical trials.

## National Institute of Environmental Health Sciences (NIEHS)

### Senate Significant Items

#### Item

***Alternative Methods of Testing*** - The Committee supports the implementation of the National Research Council's report, "Toxicity Testing in the 21st Century: A Vision and a Strategy," to create a new paradigm for risk assessment based on use of advanced molecular biological methods in lieu of animal toxicity tests. The Committee urges the NIH to play a leading role by funding relevant intramural and extramural research projects. Current activities at the NIEHS, the NIH Chemical Genomics Center and the Environmental Protection Agency show considerable potential, and the NIH is strongly encouraged to explore additional opportunities to augment this effort. (p. 109)

#### Action taken or to be taken

The NIEHS/National Toxicology Program (NTP) is collaborating with the U.S. Environmental Protection Agency (EPA), and the intramural NIH Chemical Genomics Center (NCGC) to develop a new paradigm of predictive toxicology called "Tox21." The goals of this program are to investigate the use of new tools to (1) prioritize compounds for further toxicological evaluation, (2) identify mechanisms of action, and (3) better predict human health effects. In July 2010, a new five-year Memorandum of Understanding was announced that includes expansion of the U.S. Tox21 Initiative with the U.S. Food and Drug Administration joining as a new partner. By sharing expertise, capabilities, and chemical information, we will gain a deeper understanding of chemical hazards.

The NIEHS/NTP has completed Phase I quantitative high throughput screening (qHTS) at the NCGC, which involved the screening of 1,408 substances in over 70 biochemical and cell-based assays. These assays examined the ability of compounds to damage DNA, induce various cellular stress response pathways or cell death, or act as potential endocrine disruptors. In addition, NIEHS/NTP completed screening of the 309 compounds used in EPA's ToxCast Phase I program - a Tox21 resource – for their ability to inhibit the development and growth of the roundworm, *Caenorhabditis elegans*, a multicellular model system. The completion of these screens establishes a foundation for a better understanding and improved prediction of how chemicals affect human health and the environment.

The following ongoing and planned Tox21 collaborations illustrate specific efforts to revolutionize the current approach to chemical risk assessment.

- In collaboration with the NCGC and the EPA National Center for Computational Toxicology (NCCT), the NIEHS/NTP has almost completed constructing a compound library of more than 10,000 substances that will undergo screening at the NCGC, initially in various endocrine disruptor and stress response pathway

assays. Approximately one-third of this compound library consists of approved drugs in order to better link *in vitro* data to human responses.

- NIEHS/NTP established an interagency agreement whereby the EPA NCCT will include 50 compounds of interest to the NTP among the compounds that will be included in its ToxCast Phase II program. This effort will result in an ability to compare data for more than 700 compounds (including drugs that failed in clinical trials) screened in more than 400 *in vitro* assays. This approach, while more limited in terms of the numbers of compounds that can be screened at the NCG, greatly expands the types of endpoints being evaluated by focusing on more complex assays.
- In Spring 2010, NIEHS awarded Small Business Innovative Research contracts to five small businesses for development of new screening assays and informatics tools to support Tox21 efforts.
- NIEHS/NTP has explored the identification of cellular pathways potentially involved in autism using bioinformatic tools and various databases. This information was shared with attendees at the NIEHS-sponsored workshop “Autism and the Environment: New ideas for advancing the science,” held September 8, 2010 at the NIEHS in Research Triangle Park, NC.
- NIEHS/NTP and EPA tested the endocrine disrupting chemical bisphenol A (BPA) in a number of different qHTS assays to identify cellular and molecular targets that might facilitate a better understanding of its potential impact on human health and disease. This information was shared with researchers working on BPA at a grantees meeting held September 21-22, 2010 at the NIEHS in Research Triangle Park, NC.
- In September 2010, NIEHS/NTP acquired DrugMatrix®, the world’s largest existing molecular toxicology reference database and informatics system, from Entelos, Inc, with the goal of making the database public in order to facilitate the integration of genomics data into hazard characterization. This database is a unique reference set of gene expression profiles for therapeutic, industrial, and environmental chemicals linked to classic pharmacology, toxicology, and clinical pathology measurements. The acquisition included corresponding frozen tissues from each animal used in these studies, which greatly expands the ability of the NTP to correlate genomic changes with compound-induced organ-specific toxicity.

Item

**Endocrine Disruption** - The Committee urges the NIEHS to continue to increase its research in the effects of endocrine disrupting chemicals on women's health outcomes. The Committee requests an update on these efforts in the fiscal year 2012 congressional budget justification. (p. 109)

#### Action taken or to be taken

NIEHS continues to support a wide variety of studies on the effects of endocrine disrupting chemicals (EDCs) and is highly committed to its investment in this area. NIEHS invested approximately \$14 million in Recovery Act funds on research on bisphenol A (BPA). This research builds upon existing NIEHS-funded research and National Toxicology Program (NTP) projects to resolve uncertainties and provide a better understanding of the potential risks that exposure to BPA poses to public health. One study is looking at gender-specific impacts that developmental exposure to BPA has on heart health later in life. Other studies relevant to women's health are looking at the role of fetal exposure to BPA and later effects on immune-mediated diseases (which affect women disproportionately), cancers, and metabolism and obesity. A January 2011 workshop sponsored by the NTP will evaluate the strength, consistency, and biological plausibility of findings reported in humans and experimental animals for certain environmental chemicals including arsenic and cadmium, polychlorinated biphenyls (PCBs), DDT and its metabolite DDE, other organohalogenes, BPA, phthalates, and organotin, specifically in relation to their potential as contributing factors to the epidemics of diabetes and obesity.

NIEHS-funded researchers measured the flame retardants polybrominated diphenyl ethers (PBDEs) and thyroid hormone levels in 270 pregnant women. Results showed that women with higher levels of PBDEs had lower levels of thyroid stimulating hormone, which is important because maternal thyroid hormones play a critical role in fetal brain development. Future studies will examine whether subclinical hyperthyroidism and maternal exposure to PBDEs are associated with adverse pregnancy outcomes such as preeclampsia, premature birth, and low birth weight. Researchers of the Breast Cancer and Environment Program continue to follow a cohort of over 1,200 black and Latina pubertal girls to determine the effects of hormonally active environmental exposures on pubertal endpoints such as growth, breast development, height velocity, age at menarche, menstrual cyclicity, and other intermediate factors associated with breast cancer risk.

Endocrine disrupting chemicals (EDCs) are a group of structurally diverse compounds that include pharmaceuticals, dietary supplements, industrial chemicals, and environmental contaminants. EDCs can elicit a number of adverse health effects such as hormone dependent cancers, reproductive tract abnormalities, compromised reproductive fitness, and impaired cognitive abilities. A multidisciplinary research collaborative is elucidating the pathways, networks, and signaling cascades perturbed by EDCs using toxicology, molecular biology, endocrinology, multinuclear NMR spectroscopy, data management and advanced data analysis to fully assess the potential adverse effects of synthetic and natural EDCs.

#### Item

***Sister Study and Breast Cancer*** - The Committee requests an update on this important study in the fiscal year 2012 congressional budget justification. (p. 109)

#### Action taken or to be taken

The NIEHS Sister Study is examining prospectively environmental and familial risk factors for breast cancer and other diseases in a recruited cohort of over 50,000 sisters of women who have had breast cancer. These sisters have about twice the risk of developing breast cancer as other women. The frequency of relevant genes and shared risk factors will be greater among sisters, increasing the statistical power of the study to detect risks.

Although data for studies on breast cancer are still being gathered, already two publications from the data have importance for women's health. Researchers looked at many measures, including telomeres, DNA sequences that cap the ends of a person's chromosomes. Telomeres protect the ends of chromosomes and buffer them against the losses of important genes during cell replication; degradation of telomeres is thought to have a role in the aging process.

In one study<sup>1</sup> NIEHS epidemiologists looked at the relationship between various measures of current and past body size and telomere length in 647 women enrolled in the study. They found that women who had an overweight or obese body mass index (BMI) before or during their 30s – and maintained that status since those years – had shorter telomeres than those who became overweight or obese after their 30s. A second study<sup>2</sup> showed that longer telomere length was associated with multivitamin use.

An earlier study<sup>3</sup> looked at the association between telomere length and the perceived stress levels of 647 women enrolled in the Sister Study and found that, similar to the obesity finding, stress can also impact telomere length. Women who reported above-average stress had somewhat shorter telomeres, but women with the highest levels of stress hormones showed the most shortened telomeres. The researchers also found that the effects of stress may be stronger in women 55 years and older. The papers show that factors such as obesity and perceived stress may shorten telomeres and accelerate the aging process. These studies reinforce the need to start a healthy lifestyle early and maintain it.

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<sup>1</sup> Cancer Epidemiol Biomarkers Prev. 2009 Mar; 18(3):816-20.

<sup>2</sup> Am J Clin Nutr. 2009 Jun;89(6):1857-63. Epub 2009 Mar 11.

<sup>3</sup> Cancer Epidemiol Biomarkers Prev. 2009 Feb;18(2):551-60. Epub 2009 Feb 3.

#### Item

***Women's Health and the Environment*** - The Committee urges the NIEHS to increase its research in several areas of special importance to women's health: exposures that may initiate or promote autoimmune diseases; exposures associated with risk of uterine fibroids; the effects of engineered nanomaterials in consumer products, especially cosmetics and personal care products; and environmental exposures that are associated with increased time to pregnancy. (p. 109)

#### Action taken or to be taken

Research on women's health is a high priority at NIEHS, and the specific areas highlighted are all areas of active scientific inquiry. Recent research supported by NIEHS has made advancement in these areas. NIEHS has focused attention in recent years on the need to understand environmental influences on the development of autoimmune diseases, which disproportionately strike women. A study investigating systemic lupus erythematosus (SLE) in twins discordant for the disease (one with SLE, one without) provides the first evidence that large changes in the DNA methylation profile are associated with the differential onset of the disease, indicating an association with environmental effects. The study yielded a list of epigenetically deregulated DNA sequences in SLE, which may lead to a better understanding of how this disease develops. Another study showed that SLE patients have a larger amount of a specific set of chemically linked proteins and their respective antibodies in their blood than do normal controls, which may be related to the development or progression of the disease.

In evaluating the women enrolled in the Sister Study, NIEHS researchers found that a greater risk of early fibroid diagnosis was associated with a variety of early-life exposures: consumption of soy formula during infancy, maternal prepregnancy diabetes, low childhood socioeconomic status, and gestational age at birth. There are plausible biological pathways by which these early-life factors could promote fibroid pathogenesis. Another project conducted by NIEHS scientists indicated that exposure to fenvalerate, an insecticide, is a novel risk factor for uterine fibroids through molecular mechanisms that do not directly involve the estrogen receptors.

An NIEHS-funded study found dose-related increases in time to pregnancy and infertility associated with individual serum dioxin levels in women from Seveso, Italy. For every 10-fold increase in serum dioxin, a 25 percent increase in time to pregnancy was observed. These findings may have implications for fertility in industrialized areas.

NIEHS and NTP have been key players in the National Nanotechnology Initiative, focusing on the safety or potential toxicity of engineered nanomaterials. Nanoscale materials are now widely used in commerce as industrial and consumer products with very little information on their safety, although their unique physicochemical properties suggest that their toxicology may differ from materials of similar chemical composition but larger size. The NTP is engaged in a broad-based program to address this information gap. One NTP project relevant to women's health is focusing on metal oxides, specifically evaluation of nanoscale titanium dioxide and zinc oxide, due to their

presence in cosmetics and commercial sunscreens. NTP is also testing nanoscale silver, evaluating the impact of particle size on comparative toxicity compared to ionic silver. Nanoscale silver increasingly is being used in a variety of consumer products (e.g., drug, food, and cosmetic products; clothing and textiles) based on its antibacterial properties. In addition, NIEHS supports a strong portfolio of university-based research investigating the biological effects of different types of nanomaterials, especially inhaled nanoparticles.

## National Institute on Aging (NIA)

### Senate Significant Items

#### Item

**Age-related Bone Loss** - The Committee encourages research to better define the causes of frailty, age-related bone loss and fractures, and reduced physical performance, including identifying epigenetic changes, with the aim of translating basic and animal studies into novel therapeutic approaches. The prevention and treatment of other metabolic bone diseases, including osteogenesis imperfecta, glucocorticoid-induced osteoporosis, and bone loss due to kidney disease, should also be priority research areas. (p. 109)

#### Action taken or to be taken

Bone loss, frailty, and reduced physical performance are common with advancing age. NIH supports a robust and multidisciplinary program of research aimed at understanding, preventing, and treating these diverse conditions.

- The Study of Osteoporotic Fractures (SOF) in women and the Osteoporotic Fractures in Men (MrOS) study continue to provide a wealth of information about risk factors for osteoporotic fractures. Both studies will be ongoing during FY 2012.
- Longitudinal studies such as the Study of Women's Health across the Nation (SWAN), the Rancho Bernardo Study, and the Framingham Study explore an array of age-related health conditions, including osteoporosis.
- There is a growing recognition that common health problems such as diabetes, heart disease, and osteoporosis are not independent phenomena. The processes that underlie these conditions seem to interact, and NIH has recently begun to solicit research applications to identify and characterize age-related changes in factors that integrate activity influencing bone mass, as well as the various mechanisms that coordinate these signaling pathways. Studies funded under this solicitation will be active in FY 2012.
- The exciting observation that bone also has a role as an endocrine organ, regulating activities in other organs, has opened a new avenue of research aimed at understanding the integration of body composition and energy balance. Ongoing studies into the mechanisms of action of steroid hormones are designed to uncover their roles in disease, such as for glucocorticoid excess.
- With respect to conditions which predispose people to forming defective bone tissue, including chronic kidney disease, NIH supports research to develop non-invasive detection methods to monitor bone health.

- NIH supports a Metabolic Biomarkers Consortium to identify studies that will clarify the role of specific biomarkers or surrogate outcomes in evaluating potential or actual efficacy of specific interventions. Representatives of NIH, FDA academia, and industry participate. Recently, the Consortium has begun to work toward development of guidelines for the diagnosis of sarcopenia and muscle weakness and evaluation of treatment outcomes. The purpose of this project is to develop valid outcome measures that would be acceptable to FDA and others for the evaluation of claims for interventions focused on physical disability and/or loss of muscle mass; such measures will facilitate clinical research in these areas. Investigators on several longitudinal studies met in March 2010 to develop an approach to the initial data analysis and to plan a schedule for data sharing and review.
- The goal of the NIA's Claude D. Pepper Older Americans Independence Centers (OAICs) is to increase scientific knowledge that will lead to better ways to maintain or restore independence to older persons. Each Center has a unique focus, and several Centers focus on identifying ways to ameliorate age-related loss of function. In FY 2010, three OAICs were renewed and one new Center was funded; this completed a planned expansion to 12 OAICs. This important program will be active through FY 2012.

#### Item

***Behavioral Economics*** - The Committee is pleased with the NIA's focus on this emerging area of research, which is yielding insights into the neural and behavioral underpinnings of a variety of social and economic behaviors, and the Committee encourages additional work on this topic. (p. 110)

#### Action taken or to be taken

Research using insights gained through the field of behavioral economics to improve the lives of older Americans remains an important component of NIA's overall research portfolio. In FY 2010, NIA solicited research to translate basic findings from behavioral economics into behavior change interventions, targeting health behaviors associated with chronic conditions of mid-life and older ages. To date, two awards have been made, with several more expected. These projects will all be active in FY 2012.

Three Roybal Centers for Translational Research on Aging focus on behavioral economics. For example, the Center at the National Bureau of Economic Research (newly funded in FY 2010) extends research on successful financial decision making to choices about health behavior and the development of new interventions that improve health outcomes and financial well-being while reducing costs. The PENN CMU Roybal Center on Behavioral Economics and Health, also newly funded in FY 2010, conducts studies that foster the translation of approaches from behavioral economics to the improvement of health care behaviors and health care delivery for older adults. Finally, the Roybal Center for Financial Decision Making at the Rand Corporation seeks to understand how people reach decisions about issues affecting their economic status in

old age and inform how public policy can educate or help people align decisions with their long-term objectives. All three of these Centers will be active in FY 2012.

Recognizing the enormous impact that behaviors have on health as well as health care use and delivery, the NIH Director, through the NIH Division of Program Coordination, Planning, and Strategic Initiatives and the NIH Common Fund, has launched two new programs that address behavior and health economics. The Health Economics program, launched in the wake of national health care reform, supports economic analyses of prevention-based health behaviors to establish the most cost-effective and cost-beneficial behaviors for improving health, as well as the use of behavioral economics perspectives to identify and evaluate strategies to overcome behavioral obstacles to implementation of interventions that have favorable cost-benefit ratios. The NIH Science of Behavior Change program (led by NIA) supports studies to improve understanding of basic biological and neurological mechanisms of behavior and motivation that play a role in initiating or maintaining a broad range of health-related behaviors that impact health and well-being such as substance addition, exercise habits, and weight gain.

#### Item

***Demographic and Economic Research*** - The Committee urges the NIA to continue to invest in its demographic research portfolio, particularly large-scale longitudinal studies such as the Health and Retirement Study. The Committee also urges the NIA to continue working with other Federal agencies, including the Fogarty International Center, to support and expand its investment in national and international demographic research projects. (p. 110)

#### Action taken or to be taken

Global trends in population aging are transforming the world, leading to profound changes in the social, economic, and public health arenas. NIA remains committed to the study of demographic and economic research in aging at both the national and global levels. Large-scale longitudinal studies such as the Health and Retirement Study (HRS) are a mainstay of this program. In FY 2010, funding under the American Recovery and Reinvestment Act (ARRA) facilitated the expansion of the HRS to increase minority participation, repeat collection of biomarker and psychosocial data to analyze changes in these measures over time, conduct genome-wide association studies to identify potential genetic risks and influences on a broad range of health conditions as well as social and behavioral aspects of normal aging, and conduct pilot research on methods for diagnosis of dementia, cognitive impairment without dementia, or normal cognition. Similar surveys are ongoing in 20 European countries and Asia (including China, Japan, and India), with a Mexican study pending. A major effort is currently underway to enhance cross-comparability of these surveys and facilitate innovative cross-national research.

NIA also works with other federal agencies to support national and international demographic research projects. For example, NIA participates in an interagency agreement with the World Health Organization (WHO) to support the WHO Study on

Global AGEing and Adult Health, a longitudinal study of health and health-related outcomes and their determinants in China, Ghana, India, Mexico, the Russian Federation, and South Africa. The NIA has also supported research on adult health and aging within the INDEPTH network of demographic surveillance sites in low income countries. In addition, NIA supports the International Data Base through an interagency agreement with the U.S. Census Bureau. This database contributes to a consistent, systematic, quantitative comparison of older populations in various countries and is featured in, for example, the series of publications on the Aging World that Census develops for the NIA.

NIA and the Fogarty International Center (FIC) collaborate on programs and projects in areas in which our missions intersect. For example, in one ongoing study, a team of researchers from the United States and China is studying recent developments in China's institutional elder care sector and developing a data collection instrument that can be readily used in nursing homes throughout the country. Using this instrument through structured surveys, quantitative data on the organizational attributes and resident characteristics will be collected from a representative sample of elder care homes in two major cities in China.

Finally, in 2010, NIA indicated plans to spend more than \$36.7 million over five years to support and expand its Centers on the Demography and Economics of Aging. The Centers form a network of universities and organizations leading innovative studies on the characteristics of the aging population. Nearly all of these centers are involved in international projects, helping to develop the fields of demography and economics of aging in many countries. The awards renewed support for 11 Centers and established three new ones, including one two-year ARRA-funded Center.

#### Item

***Roybal Centers for Translational Research on Aging*** - The Committee urges the NIA to continue supporting these important centers. (p. 110)

#### Action taken or to be taken

The Roybal Centers for Translational Research on Aging are supported by the National Institute on Aging (NIA) with co-funding from the National Institutes of Health Office of Behavioral and Social Sciences Research, the Agency for Healthcare Research and Quality, the Social Security Administration, and the National Institute on Disability and Rehabilitation Research in the Department of Education. These successful Centers are designed to move promising social and behavioral basic research findings into programs, tools, practices, and policies that will improve the lives of older adults and the ability of society to adapt to an aging population. The Centers currently focus on the following topics: social networks and health; extending behavioral economic approaches to financial decision making about health; older drivers; health and mobility; disease and pain management; decision making and behavior change; developing better measures of subjective well-being for use in policy decisions; and the consequences of biomedical developments for health and Medicare expenditures.

The number of Roybal Centers has increased since the program's establishment in 1992, from six original centers to 13 – one of which was established using ARRA funds – upon the program's most recent renewal in 2009. This important program will continue to be active in FY 2012.

## National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS)

### Senate Significant Items

#### Item

**Bone Loss** - The Committee urges support for research into the pathophysiology of bone loss in diverse populations in order to develop targeted therapies to reduce fractures and improve bone density, bone quality and bone strength. (p. 110)

#### Action taken or to be taken

Osteoporosis is one of the most prevalent bone diseases and is characterized by low bone mass and structural deterioration of bone tissue, affecting many people as they age. In the United States today, 44 million Americans suffer from this disease or are at risk of developing it, resulting in 1.5 million fractures annually.

The NIAMS has invested in genome-wide association studies to identify biomarkers for various diseases, including osteoporosis. Scientists in the United States have partnered with researchers in the Netherlands, Iceland, Canada, the United Kingdom, and Greece to combine bone mineral density (BMD) and genomic data from more than 19,000 people. This collaboration has enabled the researchers to detect 20 single nucleotide polymorphisms, or SNPs, which were consistently associated with variation in BMD. The results suggest that certain SNPs confer increased risk for low bone mass and fracture, and that the total number of “risk SNPs” in an individual’s genome can be a useful predictor of bone health.

Diet also plays a significant role in bone loss. Starvation, particularly during childhood and adolescence, poses osteoporosis risks by decreasing several hormones important for bone development, and at the same time increasing fat content in the bone marrow. Recently, NIAMS-funded researchers, who were in part supported by funds from the American Recovery and Reinvestment Act (ARRA), demonstrated the deleterious effects of caloric restriction on the overall bone health of juvenile mice.

Another study supported by the NIAMS showed that blood glucose levels are controlled through biochemical loop involving insulin and a bone growth protein called osteocalcin. This insight indicates that it may be possible to use osteocalcin as a therapeutic agent in the treatment of diabetes. In addition, because of the role of bone resorption in this process, it will be important to assess the impact of antiresorptive drugs, currently in wide use to prevent osteoporosis, on the control of blood glucose.

Specific risk factors for osteoporosis and patterns of fractures in men are not completely understood. Although women have an increasing prevalence of wrist fractures as they age, the wrist is not a common site of fracture in aging men. Using the long-standing NIH-funded Osteoporosis in Men (Mr. OS) cohort that followed nearly 6,000 participants over an average period of 6.2 years, researchers identified the rib as a previously unrecognized, yet common, site of fractures in elderly men. These results suggest that

rib fracture can be used as an independent predictor of higher fracture risk in the future, and can be considered an indicator of osteoporosis, for future intervention strategies.

#### Item

***Epidermolysis Bullosa (EB)*** - The Committee is aware that EB is a group of heritable skin-blistering conditions for which there is no cure. The Committee commends NIAMS for its support of EB research and encourages continued and enhanced efforts to address this painful and disabling condition. (p. 110)

#### Action taken or to be taken

Epidermolysis bullosa (EB) is a group of severe hereditary blistering skin diseases. Patients also may experience damage to other tissues and organs - including the eyes, esophagus, gastrointestinal and urinary tracts, and muscles. An estimated 12,000 Americans suffer from the disease, which is disabling for young adults with less severe forms, while more severe forms can be fatal in early infancy or in childhood.

NIAMS supports diverse research efforts that may lead to promising treatments for EB. A new method of gene therapy to correct the EB defect was investigated by NIAMS-supported scientists. A significant challenge for this approach is the potential complications of viral-based DNA transfer. However, this team was able to demonstrate sustained correction of the abnormality in affected cells. In another study, researchers were able to demonstrate the use of genetically corrected cells to facilitate the healing of wounds in one form of severe EB (recessive dystrophic EB) that usually results in deformity and death in early adulthood. This methodology potentially provides a better way to heal the wounds of this type of EB, although it is not a permanent or long lasting cure. These studies indicate progress in providing potential treatments for different forms of EB. They also establish evidence for the success of potentially safer methods of gene therapy in the treatment of skin and other diseases.

Other research findings have suggested that the risks to children with a less severe form of EB – epidermolysis bullosa simplex (EBS) – may be minimized with prenatal testing that enables doctors to diagnose unborn babies with EBS. These tests identify mutations in the genes for keratin; families of proteins that help maintain cell shape and strength, as early as the 10th week of pregnancy. Prenatal testing would enable doctors to diagnose unborn babies with EBS and take special precautions at delivery.

NIAMS recently used funds provided by the American Recovery and Reinvestment Act (ARRA) to support a project on protein therapy for recessive dystrophic epidermolysis bullosa (RDEB). This type of EB is caused by defects in the human gene encoding type VII collagen (C7), the major component of the protein that provides the anchor to the upper layer of the skin. Building off of previous work that showed therapeutic success with preclinical animal models, researchers plan to attempt C7 protein therapy in RDEB patients, and determine the safety and efficacy of this treatment. In a similar effort, another group of NIAMS-funded researchers are working to graft genetically corrected skin cells back into RDEB subjects in a human gene transfer clinical trial. Both efforts

could lead to practical therapies for RDEB, and may provide a proof of principle for using protein therapy for other debilitating skin diseases.

#### Item

**Marfan Syndrome-** The Committee commends NIAMS for its continued support of collaborative, multi-investigator research related to Marfan syndrome and encourages expanded support for research on the orthopedic manifestations of the disease. (p. 110)

#### Action taken or to be taken

Marfan syndrome is a heritable condition that affects the connective tissue that holds the body together and provides a framework for growth and development. In Marfan syndrome, the connective tissue that is found throughout the body is defective and does not act as it should, adversely affecting many body systems, including the skeleton, eyes, heart and blood vessels, nervous system, skin, and lungs. Since Marfan syndrome impacts the long bones of the skeleton, a person's arms, legs, fingers, and toes may be disproportionately long in relation to the rest of the body. Other skeletal problems include a sternum (breastbone) that is either protruding or indented, curvature of the spine (scoliosis), and flat feet.

Currently, NIAMS supports a project that focuses on the bone physiology that is central to the characteristic skeletal manifestations of Marfan syndrome. The long-term goal of this project is to generate information that will benefit the design of therapies for bone mineral replacement in patients. Some of the funds provided by the American Recovery and Reinvestment Act are being used for this effort. In addition, NIAMS supports a broad portfolio of connective tissue biology and orthopaedics research. Advances in these programs could help to inform the field of Marfan research and, ultimately, improve the quality of life of patients. NIAMS encourages Marfan investigators to engage colleagues within these communities in order to explore new areas of research and collaboration focused on the orthopaedic manifestations of the disease.

#### Item

**Outcomes Measurement-** The Committee notes with approval the success of the NIAMS-led PROMIS initiative, which aims to revolutionize the way patient-reported outcome tools are chosen and used in clinical research and practice. (p. 110)

#### Action taken or to be taken

The Patient-Reported Outcomes Measurement Information System (PROMIS®) is an NIH initiative that has, and continues to create, psychometrically-robust patient-reported banks of questions to measure symptom and quality of life outcomes. These questions are based on the World Health Organization model of physical, mental, and social health. These outcomes, such as pain, fatigue, anger, depression, anxiety, sleep, physical functioning, psychosocial illness, and others span across a wide range of disorders. Each item and questionnaire bank are rigorously evaluated both qualitatively (e.g., with patient and expert input) and quantitatively, and subsequently refined based on studies involving not only patients with a broad array of diseases (e.g., cancer, arthritis, heart disease) but also people without disease. The questions can be

administered in a variety of ways, including state-of-the-art computerized adaptive testing. These questions and assessment tools are intended to provide clinicians and researchers access to efficient, precise, valid, and responsive adult- and child-reported measures of health status.

The PROMIS initiative is funded through the NIH Common Fund and managed by the Office of the NIH Director, NIAMS, and NCCAM. The PROMIS Network of clinicians, clinical researchers, and measurement experts is organized around twelve primary research sites (PRs) and three centers that facilitate logistical coordination and support. They also provide outreach to external stakeholders, expertise in statistics and measurement science, and support for dynamic or static data collection, both on and offline. The PRs and Centers work closely with NIH project scientists, currently representing 12 NIH Institutes and Centers.

#### Item

**Scleroderma** - The Committee continues to prioritize research on scleroderma and commends NIAMS for its work in this area. The Committee requests an update on the scleroderma research portfolio as part of its fiscal year 2012 budget request. (p. 110)

#### Action taken or to be taken

Scleroderma is a complex group of diseases involving abnormal growth of connective tissue. It may manifest as hard, tight skin, but in some individuals, systemic sclerosis may affect blood vessels and internal organs, such as the heart, lungs, and kidneys. Scleroderma is believed to be an autoimmune disease; evidence suggests that it results from a combination of genetic and environmental factors, which serve as potential targets for scientific inquiry.

The NIAMS supports a Center of Research Translation (CORT) in scleroderma, which is working to uncover the pathogenic mechanisms, especially the genetic factors, and the predictors of outcomes in scleroderma, and translate them into improved medical care for patients with this disease. In May 2010, researchers associated with this CORT published findings of a new genetic susceptibility locus on the CD247 gene for systemic sclerosis (SSc), a type of scleroderma that affects the entire body. Previous research had identified genetic factors for SSc, but as in other complex genetic disorders, researchers suspected that more factors were involved. To determine this, a genome-wide association study was needed, including a large cohort of patients and controls. This information was available from the Scleroderma Family Registry and DNA repository, which had previously been funded by NIAMS. Using this information, the researchers confirmed the previous findings and identified the CD247 gene as also being involved, demonstrating a strong autoimmune component in the disease. These findings may ultimately contribute to the development of more effective therapies for the treatment of scleroderma by targeting the complex genetic factors that lead to the disease.

Two independent research groups supported by NIAMS have discovered that a molecule called early growth response 1 (EGR-1), which regulates gene expression,

plays a central role in the development of fibrosis, a condition that characterizes scleroderma and results in hardening or stiffening of organ-supporting tissues, thereby hindering normal tissue and organ function. Although each research group used different methods to induce fibrosis in mouse models, both discovered that fibrosis resulted in elevated EGR-1 activity. Removing EGR-1 from the cells reduced the cellular fibrotic response dramatically. Thus, EGR-1 function appears to be essential for the development of fibrosis, making it a potential target for therapy for diseases like scleroderma.

Stiff skin syndrome is a heritable form of scleroderma characterized by thick and hard skin, often covering the entire body. This hardening of the skin can limit joint mobility and cause other debilitating problems. Researchers funded by NIAMS have discovered that mutations in the gene for fibrillin-1 (a protein in the extracellular matrix, a mesh of proteins that provides soft, elastic, and resilient support of the skin and other organs) are a cause of stiff skin syndrome. This finding provides a significant advance in understanding the cause of scleroderma-related disorders.

#### Item

***Temporomandibular Joint Disorders (TMJDs)*** - As the temporomandibular joint is a joint in the body, the Committee continues to believe that its inclusion in the NIAMS portfolio is clearly warranted. NIAMS scientific expertise and funding would greatly accelerate the basic and clinical understanding of this joint, which is critical to such functions as speaking, breathing, eating, swallowing and making facial expressions. The Committee calls on NIAMS to collaborate with the NIDCR to develop multidisciplinary research teams involving basic and clinical scientists to study the jaw anatomy, physiology and the complex neural, endocrine and immune systems interactions that orchestrate jaw function and trigger jaw joint pathology. NIAMS should integrate the findings from interdisciplinary studies of the structure, mechanical function, metabolism, and blood flow of bone, joints, and muscles with studies of central and peripheral neural pathways, and the endocrine, paracrine, and cytokine factors that impact upon these craniofacial structures, as a means to understanding the underlying causes of pain and dysfunction. The Committee requests a response from NIAMS, in addition to the response from NIDCR, in the fiscal year 2012 congressional budget justification. (p.110)

#### Action taken or to be taken

Temporomandibular joint disorders (TMJDs) are a group of conditions that cause pain and dysfunction in the jaw joint and muscles that control jaw movement. The NIAMS supports research studying joint physiology and disease, which could help to inform the TMJD community. For example, researchers recently reported that mechanical injury to a joint, combined with the release of cytokines (signaling proteins) from tissues other than the damaged cartilage, triggers steps that may eventually lead to osteoarthritis (OA). The results of this study in the knee suggest that interventions targeting multiple cytokines immediately post-injury may forestall or even prevent subsequent cartilage degradation in joints, including the temporomandibular joint. In a separate study, NIAMS-funded investigators have developed a novel method to evaluate the health of the cartilage surface during arthroscopic surgery. The procedure detects very early

structural changes in cartilage that are highly associated with early degeneration of cartilage, providing an opportunity for early intervention.

NIAMS also partnered with NIDCR to support the 2nd TMJ Bioengineering Conference which took place in November 2009. As a follow-up to the 2006 meeting, the goals were to facilitate communication and build collaboration among the previously disparate communities involved in TMJDs. Topics discussed at the meeting were cartilage and osteochondral biomechanics and tissue engineering, as well as imaging, pain, and inflammation as they relate to the temporomandibular joint. NIAMS also encourages investigators studying TMJDs to engage colleagues and experts in related fields to form collaborative teams that could lead to the development of new diagnostic and treatment techniques.

NIDCR supports research on the biology of joint function and disorders of the temporomandibular joint. NIDCR has several scientific programs that directly impact the Institute's focus on TMJDs. The Mineralized Tissue Physiology Program supports basic research on the physiology of craniofacial bone and cartilage and the dysfunction of these tissues leading to pathology. The Tissue Engineering and Regenerative Medicine Program supports interdisciplinary research that develops replacement tissues that mimic the structure and function of bone, cartilage, muscle, vascular and nervous system components of the temporomandibular joint. The Molecular and Cellular Neuroscience Program supports research that focuses on normal and aberrant function of the temporomandibular joint. It also supports research on chronic pain associated with TMJDs. This Program supports studies on neural system function and the role of interactions of the nervous system with the immune and endocrine systems in disease. NIDCR has recently developed a five-year plan for TMJDs that will stimulate research driven by new findings from human genomic studies. NIDCR collaborates with other NIH Institutes through trans-NIH groups such as the Pain Consortium and the Blueprint for Neuroscience Research to augment its research support for TMJDs.

## National Institute on Deafness and Other Communications Disorders (NIDCD)

### Senate Significant Items

#### Item

***Early Detection and Intervention*** - The Committee urges continued support for research on early detection, diagnosis and intervention of children with hearing loss. The NIDCD is encouraged to fund studies that follow speech, language, voice and auditory behavior outcomes for children identified early in life and for children using various hearing devices and interventions. ( p.111)

#### Action taken or to be taken

Approximately 2-3 in every 1000 children in the United States are born with severe to profound deafness. In 1989, less than five percent of newborns received hearing screening prior to leaving the hospital and most children were not identified to have a hearing impairment until 2-3 years of age. This delay during a critical period for language development led to lifelong difficulties in language acquisition and the need for costly special education in schools for the deaf.

The implementation of universal newborn hearing screening, a joint effort by NIDCD and other federal agencies, has dramatically improved the identification of infants with hearing loss early in life and accelerated the initiation of services for these children. Today, more than ninety-five percent of children are screened for hearing loss shortly after birth. NIDCD continues to examine the outcomes of children identified through newborn hearing screening. For example, NIDCD-supported scientists are working to identify optimal sound amplification strategies for children identified through these programs. The studies are examining multiple potential hearing aid acoustical fittings to determine their effect on speech perception and understanding, and how complex listening environments (i.e., noisy classrooms) may impact hearing aid performance. In addition, NIDCD-supported scientists are also exploring the psychosocial outcomes of children with mild to severe hearing loss, correlating not only the child's performance and learning, but also how parental engagement and support and services delivery affect the long-term emotional well-being of the child.

The number of hearing impaired children who were identified by newborn screening programs and receive a cochlear implant prior to two years old is increasing. These children are now making their way into mainstream classrooms. However, there is significant variability in the speech and language outcomes of children who receive cochlear implants. NIDCD-supported scientists are examining the neurological basis of these differences. By understanding the fundamental brain differences that affect cochlear implant outcomes, better clinical management strategies can be developed to support those children at risk of poor clinical outcomes. In addition, the challenges of learning in mainstream classrooms may differ for children using hearing aids versus cochlear implants. One project will be following a cohort of normal hearing children and children with hearing loss first examined during the preschool years for language

acquisition strategies, as they enter the early elementary school years. This will allow scientists to determine which intervention strategies in the preschool years best prepare children for the language demands of mainstream classrooms in the early elementary school years.

#### Item

**Hair Cell Regeneration** - The Committee continues to place a high priority on research involving hair cell regeneration and stem cells. (p. 111)

#### Action taken or to be taken

Hair cells are the specialized cell of the inner ear which converts sound into electrical signals which the brain perceives. The death or damage to these cells through either environmental insults or as a part of the aging process, leads to sensorineural hearing loss. These specialized cells are not able to regenerate in mammals, making the hearing loss permanent. The NIDCD places a high priority on studies involving both hair cell regeneration and stem cells. The current NIDCD strategic plan includes goals on hair cell regeneration and the use of stem cells to understand normal and diseased states in the hope of developing improved therapies for individuals with communication disorders.

NIDCD-supported scientists are seeking a better understanding of the normal mechanisms that control development of hearing because that information will be critical for developing methods to regenerate hair cells. As part of this effort, NIDCD-supported scientists are developing *in vitro* assays to identify molecules involved in the differentiation of both adult and embryonic stem cells into specific cell types used in communication.

In May of 2010, NIDCD-supported scientists announced that they had developed a system for making what appear to be functional hair cells from stem cells. The findings bring the scientists closer to achieving two goals. Their short term goal is to grow abundant numbers of working hair cells for further research. Their long-term goal is to use what they discover to restore hair cells within the ear.

The ability to re-grow hair cells will be an outstanding achievement. However, hair cells alone will not restore hearing unless they are properly reconnected with the parts of the brain that process sound. NIH-supported scientists found that replacement hair cells and nerve cells successfully establish connections in an organized way, although the nerve endings are simpler than those generated during normal development. They are now working to stimulate the simple nerve endings to become more elaborate, and thus more mature. This research will help scientists understand how to regenerate connections between nerve cells that project to the brain and replacement hair cells.

Within the inner ear, neurons connect sensory hair cells to hearing centers in the brain. NIDCD Intramural scientists recently demonstrated that transcription factors (proteins that bind DNA and initiate its copying) are able to induce some non-sensory cells within the cochlea to develop as neurons. These results suggest that it may be possible to

induce the formation of inner ear neurons using gene transfer. This method could help scientists develop therapies to induce new inner ear neurons in individuals who have lost them as a result of genetic mutation or trauma.

#### Item

***Hearing Aids and Cochlear Implants*** - The Committee strongly encourages the NIDCD to support research to make hearing aids more accessible to the millions of Americans with mild to moderate hearing loss. It urges investigative collaborations into low-cost hearing aids between industry, scientists, clinicians and consumers so that more of the population who need hearing aids can obtain them at affordable costs. Regarding cochlear implants, the Committee recognizes the need to study the expansion of electrical speech processing in children and adults, and to conduct research into mechanisms of acoustic hearing loss in subjects using acoustic plus electric speech processing. (p. 111)

#### Action taken or to be taken

Approximately 17 percent of American adults (36 million people) report having some degree of hearing loss. Nearly half of adults aged 75 years and older have hearing loss. The hearing aid is the primary device available for managing hearing loss. Despite significant improvements in hearing aid technology over recent decades, only 20 percent of Americans who could benefit from hearing aids actually use them. Even among hearing aid users, most have lived with hearing loss for more than ten years before seeking a hearing instrument and their impairment has progressed to moderate-to-severe levels. This is due to many reasons, including the perceived and actual benefits, cost, stigma, value (benefit relative to price) of hearing aids, and accessibility to hearing health care. Acting on recommendations emerging from a 2009 NIDCD Working Group on Accessible and Affordable Hearing Health Care for Adults with Mild to Moderate Hearing Loss, the NIDCD has launched a series of research initiatives. These initiatives facilitate research collaborations between clinicians and researchers in academic and industry settings, seeking to address the pressing public health need of improving the accessibility, affordability, and outcomes of hearing health care. To date, five funding opportunity announcements have been issued.

In addition, the cochlear implant constitutes a great advance in the management of severe-to-profound hearing loss. It is the most widely utilized neural prosthetic device worldwide. The NIDCD has a long history of supporting the development of the cochlear implant. Recently, NIDCD-supported scientists have investigated alternative strategies for optimizing the selection and fitting of cochlear implants to markedly hearing-impaired individuals having predominantly high frequency hearing loss and appreciable residual low frequency hearing (“ski-slope” audiogram cases) in the better ear. Research is underway evaluating the “bimodal” fitting alternative, involving a cochlear prosthesis implanted in one ear and a hearing aid fitted to the other ear. A more recent fitting strategy, under active clinical study, is combining electrical and acoustical stimulation of the same ear through implanting a short electrode. This allows preservation of residual hearing in the lower frequencies and the possibility of acoustical stimulation concomitant with electrical stimulation. This approach has been shown to improve speech

understanding in noisy backgrounds and the appreciation of music in some individuals. While this research is still in process, the NIDCD is hopeful that it will provide hearing professionals with alternatives to optimize the performance of hearing prostheses for select individuals.

#### Item

**Noise and Environmentally Induced Hearing Loss** - The Committee recognizes that while there is increasing susceptibility to noise and environmentally induced hearing loss as one ages, young individuals are also at risk. The Committee urges the NIDCD to study how to identify school-age children with sound-induced hearing loss and address its negative consequences on their academic achievements and social interactions. It understands the potentially deleterious effects of noise and environmental pollutants in water and air on the inner ear's hair cells, synapses and auditory nerve and encourages studies of protective agents. It recommends research, including proteomic studies, to identify, characterize and prevent effects of toxicants, including such chemicals as lead, mercury and carbon monoxide on hearing, especially during aging, and during prenatal and early postnatal development. The Committee also commends the NIDCD for its efforts to raise public awareness of the omnipresent threats to the auditory system posed by environmental noise. (p.111,112)

#### Action taken or to be taken

School-age children with hearing loss (HL) are at risk for poorer academic outcomes. While little is known about noise induced hearing loss (NIHL) in school-aged children, at this time, there is no evidence that children with NIHL will manifest future academic/ learning problems any differently than children with hearing loss due to some other reason (infection, genetics, unknown etiology). NIDCD-supported scientists are examining students with unilateral HL (UHL, only one ear affected), as well as seeking to address remediation in all children with hearing loss, irrespective of the mode of injury. Previously, it was believed that children with UHL would have little academic consequences as speech and language acquisition could be accomplished through the hearing ear. However, recent studies have suggested that children with UHL are at increased risk for educational and/or behavioral problems. This study seeks to determine what contributes to this risk, and what strategies could be employed to minimize the risk. Additionally, NIDCD-supported scientists are examining college-age students to develop a risk profile of developing NIHL. The project will examine factors such as genetics, noise exposure, and audiological profile to better understand the susceptibility of adolescents and young adults to develop NIHL.

Protecting individuals from NIHL is also a priority for NIDCD. NIDCD-supported scientists are exploring the role of a protein, a particular calcium channel pump, in the inner ear and auditory brainstem, and how environmental exposures and genetic predisposition combine to contribute to hearing loss. This research may one day lead to new drugs which protect against damage. In addition, other NIDCD-supported scientists are exploring the use of combinations of FDA-approved drugs to inhibit multiple molecular pathways that lead to inner ear damage and thereby, hearing loss. This combination therapy approach is already in use to treat other diseases such as cancer

and HIV/AIDS. If successful, these preventative treatments may be successfully given to individuals who are exposed to hazardous levels of noise regularly. Finally, NIDCD-supported scientists have demonstrated that a combination of micronutrients (antioxidants and other agents) prevent NIHL in animals by attenuating sensory cell death in the inner ear. A current phase II clinical trial investigates whether these agents can prevent NIHL.

NIDCD-supported scientists are examining utilizing the Zebrafish lateral line model system to assess the development of and toxicant-induced damage to sensory hair cells. Through genetic and proteomic observations, the scientists are identifying the molecular cascades that occur after hair cells are exposed to ototoxic agents, and screening for agents that protect against damage.

NIDCD thanks the committee for recognizing our public education efforts about the dangers of noise exposure. One campaign, "It's a Noisy Planet. Protect Their Hearing," reaches out to parents of tweens, children between 8 and 12 years old, to educate them about NIHL. Recently, NIDCD expanded the campaign to include Spanish language publications.

#### Item

**Otitis Media** - The Committee recognizes the threat to infants' and children's health and development from ear infection. The Committee therefore urges the NIDCD to accelerate its support to investigate the pathogenesis of ear infection and its consequences. Studies should include identification of genetic risk factors; new treatments for chronic and recurrent otitis media; new methods for delivery of drugs to the middle ear; and development of vaccines. (p. 112)

#### Action taken or to be taken

Parents of infants and toddlers have become accustomed to recognizing the signs and symptoms of middle ear infections, or otitis media (OM): irritability, tugging at ears, loss of appetite, loss of sleep, pain, or fever. OM is one of the most common reasons for a sick infant to visit a doctor. Seventy-five percent of children experience at least one episode of OM by their third birthday. Almost half of these children will have three or more ear infections during their first three years. The medical costs and lost wages resulting from OM amount to billions of dollars in the U.S. each year. Although OM is primarily a disease of infants and young children, it can also affect adults. Otitis media often begins when viral or bacterial infections that cause sore throats, colds, or other respiratory or breathing problems spread to the middle ear. The NIDCD supports research to demonstrate and confirm the role of genetic factors in the development of chronic and recurrent OM. One of the goals of this study is to identify susceptibility genes by performing a detailed analysis of genes associated with OM in both families and individuals. It is anticipated that this study will provide new insights into the gene-gene and gene-environment interactions that contribute to the development of OM in childhood.

The NIDCD also supports a wide variety of studies examining ways to develop new treatments for chronic and recurrent OM. These studies involve efforts to examine 1) antimicrobial peptides and innate immunity, 2) bacterial pathogenesis and human immune responses following infection, and 3) the role of bacterial virulence factors and host defense using mutant strains and immunization experiments to facilitate the development of new strategies for prevention and treatment of otitis media and its complications, especially significant in the era of multi-drug resistant bacteria. Further, the NIDCD supports research to develop new methods for delivery of drugs to the middle ear; and development of vaccines. For instance, NIDCD is funding a study on trans-tympanic (across the ear drum) treatment of OM. The purpose is to develop a means of treating middle ear infections by applying a gel in the outer ear, once. The chemicals in the gel will help antibiotics cross the eardrum and the gel holds the medicine in place. This approach could prevent antibiotic resistance and toxicity by keeping the medications localized. Also, NIDCD is funding studies with the ultimate intent of vaccine development. Scientists are developing better methods to manage OM, via the development of vaccines to prevent middle ear infections due to non-typeable *Haemophilus influenzae* (NTHi). Another study is examining the use of protein-based or conjugate polysaccharides for vaccines. Finally, the NIDCD plans to provide funding for the 10<sup>th</sup> International Post-Symposium Conference on Recent Advances in Otitis Media in June 2011 where investigators involved in OM research review research findings reported during the previous four years. During this conference, leaders in OM research will plan strategies and identify research gaps necessary to advance the research which will lead to treatments.

#### Item

**Plasticity** - The Committee continues to support research on functional changes of synapses of the central auditory nervous system, including the cortex, following developmental hearing loss. It encourages research that builds on understanding of the dramatic dysfunction that occurs and explores experimental approaches to restoration of normal function of these synapses. Basic research of ways to use auditory training learning tasks to restore perception in normal adult subjects and those with auditory or vestibular deficits is also recommended. (p. 112)

#### Action taken or to be taken

The NIDCD supports research specifically on neuronal and synaptic plasticity in auditory central nervous system pathways, and related to developmental hearing loss. For example, NIDCD-supported scientists are using brain imaging techniques to study children with severe-to-profound unilateral sensorineural hearing loss (in one ear). These studies will provide information on how the brain of children with unilateral hearing loss can reorganize to process sound, speech and language. If these studies determine that their brains do not easily compensate for the unilateral hearing loss, these children may need greater remediation, such as hearing aids.

To examine how the auditory cortex is changed by the loss of hearing during early development, NIDCD-supported scientists are studying a reversible animal model of experimentally induced conductive hearing loss (CHL). Using a reversible animal model

of CHL, these scientists are able to observe the plastic changes in the brain during the onset of a hearing loss and when hearing is later restored. This animal model characterizes the progressive developmental expression of brain plasticity arising from CHL and will illuminate the mechanisms underlying persistent auditory processing disorders similarly observed in children with a history of CHL, such as children with frequent otitis media with effusion (ear infection with fluid trapped behind the eardrum).

The loss of sensory input to the brain that accompanies deafness produces changes in the properties of synaptic transmission in auditory neurons that alter the processing and interpretation of sounds and speech. Understanding how these changes occur, as well as how to prevent or reverse them, is of therapeutic significance for treatment of hearing disorders. NIDCD intramural scientists are studying how auditory signals are encoded and processed in the central auditory system. This research is providing insight into mechanisms of synaptic plasticity required for normal hearing function in the brain region that enables a listener to identify the location of sound sources. Planned studies using animal models of human deafness will further contribute to understanding how auditory processing is affected by hearing loss.

Profound hearing loss in children can produce long-lasting deficits in auditory perception and language acquisition, and it has been suggested that mild to moderate hearing loss, including that commonly associated with middle ear infections, might also impact auditory performance. To address this question, NIDCD-supported scientists will induce conductive hearing loss in developing animals, and study their behavioral performance and central auditory nervous system function as adults. Thus, this study will examine whether moderate hearing loss disrupts both perceptual skills and the neural coding properties that support them. In another NIDCD-supported study, animals raised with moderate early conductive hearing loss are tested to see whether training on an auditory task during development can rescue normal perceptual behavior. An animal model with early conductive hearing loss is used to examine nerve function in the brain to test for association with hearing deficits in adult animals, as well as the potential for auditory training to help rescue hearing perception.

#### Item

**Presbycusis** - The Committee urges the NIDCD to continue its support of physiological and neurological studies of the peripheral and central mechanisms of presbycusis. (p. 112)

#### Action taken or to be taken

Presbycusis is the loss of hearing that gradually occurs in most individuals as they grow older. About 30-35 percent of adults between the ages of 65 and 75 years have a hearing loss. It is estimated that 40-50 percent of people age 75 and older have a hearing loss. The NIDCD considers presbycusis an area of great importance. NIDCD-support is helping scientists discover how age-related hearing loss (presbycusis) is caused by a complex interaction of inherited genes and environmental exposures. NIDCD is supporting a P50 Specialized Center on Experimental and Clinical Studies of Presbycusis. Scientists funded via this Center are using a multidisciplinary approach to

improve diagnostic, rehabilitative, and preventive measures for age-related hearing loss. One project uses neuroimaging to examine the structure and function of parts of the brain thought to contribute to age-related declines in speech recognition in older adults. Another project seeks to identify genetic mutations associated with age-related hearing loss. The team of scientists then works to determine how the mutation affects the structure and function of hearing.

Other scientists supported by the NIDCD are identifying genes that make adults more susceptible to age-related hearing loss. Their studies use a variety of techniques to identify these so-called “susceptibility genes”, including studies of inbred mice, documenting and genotyping human families with inherited patterns of hearing loss, and the use of genome-wide association studies (GWAS). Studies of families with pronounced adult-onset hearing loss have identified a mutation that makes the sensory cells of the inner ear more likely to die. Another group of scientists is developing a library of genes that are actively expressed in the human cochlea. They hope to compare differences in these particular genes in individuals with normal hearing and in those with presbycusis.

Another group of NIDCD-supported scientists have discovered that older adults today may be retaining their hearing better than in previous generations. The data also suggest that some hearing loss is due to lifestyle choices, and thus, individuals may be able to change their habits to preserve their hearing. The scientists are also working to determine whether adult onset diseases, such as type 2 diabetes and hardening of the arteries, play a role in age-related hearing loss.

All of these NIDCD-supported scientists are learning information about how and why human beings lose their hearing as they age. They seek to use their increased understanding to develop improved treatment and prevention methods for presbycusis.

#### Item

**Tinnitus** - The Committee commends NIDCD for hosting a multi-agency collaborative workshop to support new and expanded research into tinnitus. The Committee recommends that the NIDCD expand its research into causal mechanisms underlying peripheral and central tinnitus and pursue research devoted to preventions, treatments and cures of this prevalent disorder, which is also the largest service-connected disability for returning military personnel. (p. 112)

#### Action taken or to be taken

Tinnitus is a major health concern and its severity can range from a mild condition which requires no intervention to a severe debilitating disease with significant emotional, social and economic impact. The estimated number of number of Americans who have experienced this “ringing in the ears” is currently 25 million, but this number is expected to grow over time primarily due to an increased average age of the population. Tinnitus is also the most frequent service-connected disability of U.S. veterans returning from active duty, and more than 635,000 veterans were receiving disability compensation for tinnitus at the end of FY2009.

NIDCD continues to conduct research into the underlying causes of tinnitus, and to explore potential therapies for the treatment of affected individuals. A significant obstacle for advancement in this field remains the lack of knowledge about the specific neural dysfunction(s) responsible for tinnitus. NIDCD-supported scientists are using advanced imaging techniques to correlate the perception of tinnitus with specific patterns of neural activity in the brain. There is increasing evidence for the involvement of brain structures outside the direct pathway from the ear to the cortex, altering the classic theory that noise-induced hearing loss, followed by unknown changes in the direct auditory pathway, gives rise to tinnitus. NIDCD Intramural scientists are also exploring the neurological basis of the tinnitus perception. Scientists have performed functional and structural imaging studies on subjects with tinnitus and hearing loss, subjects with hearing loss and no tinnitus, and subjects with normal hearing. The structural scan allowed them to examine the hypothesis that brain regions, especially the auditory cortex, should show reorganization after peripheral hearing loss which may contribute to tinnitus. They will soon publish results demonstrating the structural brain changes have more to do with hearing loss than with tinnitus. In addition, functional studies suggest that the engagement of the brain's attentional network may be one of the key differences between individuals with chronic tinnitus and hearing loss and those with hearing loss without tinnitus.

While research continues to elucidate the reasons why tinnitus occurs, efforts are also underway to prevent and treat the condition. NIDCD-supported scientists are identifying chemicals that could disrupt the processes that lead to chronic tinnitus. Since tinnitus is often associated with hearing loss, scientists are examining how ototoxic drugs affect the hearing system and using that knowledge to develop better drug delivery methods that could prevent tinnitus. Behavioral and environmental interventions are also being explored. These include the use of tinnitus maskers, white noise machines that distract attention from the tinnitus sensation, behavioral therapies, or a combination of the two to decrease the impact of tinnitus on daily life. Drug treatments that suppress the hyperactivity of the hearing system are another option currently being explored. Finally, brain stimulation techniques are under evaluation. These techniques may be non-invasive (not requiring surgery) or invasive (requiring the implantation of electrodes into the brain).

#### Item

***Vestibular Research*** - The Committee continues to urge the NIDCD to conduct vestibular research in animal models and humans to improve the diagnosis, intervention strategies and treatment of vertigo and balance disorders, including studies to prevent the severe vertigo attacks and disequilibrium associated with Meniere's disease.( p.112)

#### Action taken or to be taken

Roughly 8 million adults report having problems with balance. An additional 2.4 million American adults report having a chronic problem with dizziness. NIDCD is supporting a vigorous research program into means for diagnosing and treating vertigo and other balance disorders. These studies range from anatomical studies of the organs that

detect balance and the pathways that carry this information, to studies of how and why medications for high blood pressure cause vertigo and dizziness, and studies of how the balance organs use chemical signals to shape the information about balance that is sent to the brain. By increasing our understanding of how the inner ear senses balance and sends this information to the brain, NIDCD aims to improve the diagnosis and treatment of balance disorders such as benign positional vertigo and Meniere's disease.

NIDCD-supported scientists are studying the biomechanics of the balance organs that sense rotational motion— the semicircular canals – in their normal and diseased states. By increasing our understanding of how the semicircular canals detect and send messages to the brain about balance, they hope to develop new ways to restore an appropriate sense of balance in individuals with vestibular disorders.

One group of NIDCD-supported scientists noted that the brain pathways that carry pain to the brain are organized in a way that is similar to pathways that carry balance information, and that severe migraines (pain) and balance problems frequently co-occur. By carefully tracing both of these pathways and observing how pain medications affect the information they carry, these investigators hope to develop new ways to treat both migraine and balance problems.

Medications used to treat high blood pressure often have the unwanted side-effect of causing dizziness and vertigo, especially in elderly individuals. NIDCD-supported scientists are studying how and why these medications produce dizziness and vertigo, in the hope of developing medications for high blood pressure that do not cause these negative side-effects.

Other NIDCD-supported scientists are studying the chemical communications between the balance organs of the inner ear and the nerve cells that carry this information to the brain. By understanding how the balance organ's sensory hair cells code the information about balance before it is sent to the brain, the scientists hope to develop a way to treat individuals whose balance signals are inappropriate, such as in Meniere's disease or benign positional vertigo.

## National Institute of Mental Health (NIMH)

### Senate Significant Items

#### Item

**Children's Mental Health** - Early diagnosis, prevention, and treatment is critical for the millions of families affected by autism, attention deficit hyperactivity disorder, anxiety disorders, depression, bipolar disorder and eating disorders. The NIMH is encouraged to continue supporting clinical trials to demonstrate the evidence base for effective pharmacological and behavioral interventions and treatments for child and adolescent populations with these disorders. (p. 115)

#### Action taken or to be taken

In contrast to many other chronic medical conditions, mental disorders typically begin at an early age. According to the National Health and Nutrition Examination Survey, 13.1% of children aged 8-15 are clinically diagnosable for a mental disorder<sup>4</sup>. While we have long known that mental disorders are brain disorders, recent research has begun to re-frame these illnesses as disorders of brain development. Redefining these illnesses in terms of developmental trajectories provides unprecedented promise for the prediction and prevention of mental disorders, as well as opportunities to harness this knowledge to improve diagnosis and treatment.

Research to improve the prevention, early identification, and treatment of childhood disorders is an important area of investigation for NIMH. The Institute is highly committed to the support of research on behavioral and pharmacological interventions and the efficacy of the combined use of these interventions in different treatment populations. For example, a number of NIMH-funded projects are developing and/or testing strategies to prevent depression among children and adolescents who are at risk for the disorder. These clinical trials vary with regard to the types of intervention (e.g., cognitive, behavioral, interpersonal), location (e.g., school, employment center), and age of enrolled participants. All of the studies are focused on developing strategies that could be implemented and disseminated widely in order to reduce the public health burden of this disorder. In addition, several clinical trials are testing psychosocial interventions for the behavioral management of preschoolers with attention deficit hyperactivity disorder, as well as family-based and cognitive therapy approaches to address the symptoms of anorexia/bulimia, anxiety disorders, and bipolar disorder among children and adolescents. NIMH-funded research recently showed that adolescents with anorexia who participated in family-based therapy were significantly less likely to relapse from remission or to be hospitalized than those treated with

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<sup>4</sup> Kathleen Ries Merikangas, Jian-Ping He, Debra Brody, Prudence W. Fisher, Karen Bourdon, and Doreen S. Koretz. *Prevalence and Treatment of Mental Disorders Among US Children in the 2001–2004 NHANES*. Pediatrics, Jan 2010; 125: 75 - 81.

individual therapy<sup>5</sup>. The results of this and similar studies will inform treatment and potentially lessen the societal burden and cost of mental health disorders. NIMH continues to fund studies assessing the safety and efficacy of pharmacological treatments for mental disorders in children and adolescents. For example, NIMH-funded trials of behavioral and pharmacological interventions to manage the symptoms associated with autism spectrum disorders are currently underway. These studies will provide the empirical evidence on which to base effective interventions that, when delivered early, may beneficially impact the trajectory of illness and thus improve the long-term prognosis.

#### Item

**Behavioral Management Drugs for Children** - The committee is aware that powerful psychotropic medications are being prescribed for children as young as 5 years old. The NIMH is encouraged to expand its research to better understand the effects these medications have on the development of children, as well as to support research on treatment modalities that will lessen both provider's reliance and children's dependence on these medications for behavior management. (p. 115)

#### Action taken or to be taken

Mental disorders often manifest at an early age. According to the National Health and Nutrition Examination Survey, 13.1% of children aged 8-15 are clinically diagnosable for a mental disorder<sup>6</sup>. By predicting, detecting, and intervening early in the disease process, we can dramatically improve an individual's likelihood of a life free from the suffering of mental disorders.

Given this public health imperative, NIMH is highly committed to the support of research on both behavioral and pharmacological interventions in children as well as the efficacy of their combined use, and to the dissemination and implementation of evidence-based interventions across diverse community settings. NIMH conducts research on pharmacological, psychosocial, therapeutic, and preventive interventions to be used alone or in combination with pharmacological interventions for a variety of disorders, such as obsessive-compulsive disorder, mood disorders, and anxiety disorders in children of varying ages. For example, NIMH-funded researchers are evaluating the benefits of a psychosocial intervention for the behavioral management of young children, Parent-Child Interaction Therapy, in preschoolers (age 3-5) with attention deficit hyperactivity disorder (ADHD). Another NIMH-funded study is assessing the efficacy of a promising home-based behavioral intervention for parents of preschoolers with ADHD. A number of other NIMH-supported clinical studies are in progress to

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<sup>5</sup> James Lock; Daniel Le Grange; W. Stewart Agras; Ann Moye; Susan W. Bryson; Booil Jo. *Randomized Clinical Trial Comparing Family-Based Treatment With Adolescent-Focused Individual Therapy for Adolescents With Anorexia Nervosa*. *Arch Gen Psychiatry*. 2010;67(10):1025-1032.

<sup>6</sup> Kathleen Ries Merikangas, Jian-Ping He, Debra Brody, Prudence W. Fisher, Karen Bourdon, and Doreen S. Koretz. *Prevalence and Treatment of Mental Disorders Among US Children in the 2001–2004 NHANES*. *Pediatrics*, Jan 2010; 125: 75 - 81.

evaluate several forms of behavioral therapy aimed at preventing the onset, or reducing symptoms of, mental disorders in at-risk children.

In addition to seeking new and improved pharmacological interventions, NIMH is committed to supporting research on the safety and efficacy of the use of psychotropic medications in children and adolescents. Examples of current NIMH-funded pharmacological research in this area include two multi-site studies evaluating the benefits and safety of antipsychotic medications used to manage severe impulsive aggression in children with ADHD who are unresponsive to behavioral therapy and stimulant medication. The Institute is also supporting a systematic follow-up of children who were treated with stimulant medication for ADHD as preschoolers to inform the possible long-term effects of these medications on development.

Because of concerns about the increasing use of antipsychotic medications in children, a special workgroup was formed under the Best Pharmaceuticals for Children Act (BPCA) initiative under the coordination of the National Institute of Child Health and Human Development. The workgroup, which includes representation from NIMH and the Food and Drug Administration, has identified a number of initiatives, some of which are in progress, to better understand the effects of these medications on developing children. Through the BPCA initiative, research is ongoing that will lead to better information and labeling of drugs for pediatric use.

#### Item

***Dissemination of Research Results*** - The Committee commends the NIMH for leading a multi-Institute research initiative to identify, develop, and refine effective methods for disseminating and implementing research-tested health behavior change interventions into public health and clinical practice settings. (p. 115)

#### Action taken or to be taken

NIMH appreciates the commendation on our leadership of the trans-NIH initiative to improve the science of dissemination and implementation in health. The broad-based support for this initiative has resulted in a tremendous increase in interest and the quality of science in this area. NIH has twelve Institutes and Centers participating in this initiative, an annual scientific conference approaching a thousand participants, a standing review committee to ensure consistent review of meritorious applications across the NIH, and most importantly, a growing foundation of knowledge on how best to improve the utilization of effective health interventions in clinical and community practice settings. NIMH is pleased to report a current portfolio of approximately \$40.5 million in this research area, including individual research studies, centers, and research training mechanisms. We anticipate continued growth in this area, fueling NIH efforts to ensure that scientific discovery translates into tangible public health benefit.

#### Item

***Immigrant Health*** - The Committee recognizes that immigrants to the United States experience unique stresses, prejudice and poverty, and it urges the NIMH to direct

research on the adaptation, development, health, and mental health needs of diverse immigrant populations. (p. 115)

#### Action taken or to be taken

NIMH continues to support research on the unique mental health needs of diverse immigrant populations across a range of contexts; over multiple generations; and characterized by a variety of social, economic, and political experiences precipitating immigration (i.e., including refugee populations). NIMH-funded research addresses issues pertinent to diverse immigrant populations across the lifespan and includes a wide range of studies, such as those identifying determinants of mental illness in immigrant groups in the United States and those that seek to understand factors related to prevention, intervention, and service access and use (e.g., preventive interventions in adolescents, culturally specific barriers to care, and cultural adaptation of evidence-based treatments).

For example, one project funded by NIMH examines whether migration to the United States increases risk for mental disorders among Mexican-Americans and whether return migration or having transnational family networks increases risk among those in Mexico. This study also explores how cultural orientation affects the perception of a mental health problem as a medical concern through analysis of data on actual service use, perceived need for care, and willingness to seek treatment for mental health problems.

Two NIMH-supported projects address key issues specifically related to refugee populations. One project compares mental health over time in a random sample of newly arrived Iraqi refugees with a group of legal Middle East immigrants from other countries to understand whether institutional resources, such as language and vocational training, attenuate the health risks associated with post-displacement stress. The other study examines how family and ecological resources protect against mental health problems in at-risk refugee adolescents in order to develop a prevention intervention that is adaptable for different cultures and different service settings. Several NIMH-funded studies focus on the cultural adaptation of interventions. One project aims to determine the minimum requirements that are necessary to integrate a culturally adapted parenting intervention characterized by high feasibility, efficacy, and acceptability in low-income, first-generation Latino immigrants at high risk for intense social and familial stressors. Another study examines the process of adapting a parent training program to improve the behavioral and social-emotional health of children in Latino immigrant families. This research will enable investigators to address both the high level of unmet mental health needs and the limited scientific evidence on the development of culturally responsive interventions for this population. NIMH continues to support research that examines the social, familial, and psychological processes that may increase risk for or protect against mental illness among immigrants and refugees, as well as the factors that bear on service provision, access, and care. These studies will provide critical information for the development of culturally appropriate clinical practices, diagnostic tools, and effective interventions.

## National Institute of Drug Abuse (NIDA)

### Senate Significant Items

#### Item

**Behavioral Genetics** – The Committee encourages NIDA's continued investment in behavioral genetics, especially in studies that combine genetic and behavioral approaches. The Committee particularly commends research on the relationships among behavior, genetics and nicotine addiction, and how they impact cognitive function. (p. 113)

#### Action taken or to be taken

NIDA is committed to maintain and expand its efforts in the field of behavioral genetics. Over the past year, several new initiatives have been undertaken to further elucidate, refine, and ascribe function to highly replicated findings made through genome wide association studies (GWAS). They are:

- Deep Sequencing and Analysis of Pharmacogenomic Regions: Discovery and Analysis of Genetic Variants Contributing to Drug Abuse and Addiction—to support studies proposing to use next-generation sequencing technologies to refine further the analyses of genomic regions that have been repeatedly associated with addiction and drug abuse outcomes.
- Functional Characterization of Genetic Variants and Interactions: The Genes, Environment and Health Initiative—to support research that functionally characterizes and validates genetic variations and relates them to biological mechanisms or disease causality.
- Exploring Epigenomic Processes and Non-Coding RNAs in HIV/AIDS—to enhance our understanding of the role of epigenomics (i.e., lasting changes to DNA structure and function from exposure to various stimuli) in HIV infection and pathogenesis in combination with substance abuse.

Similarly, NIDA will continue to build upon the significant advances that have been made recently with regards to the behavioral genetics of nicotine addiction. Independent studies, in the past couple of years, have identified specific gene variants that impact smoking behaviors<sup>7</sup> and the risk of addiction as a function of age of onset. In addition, genetic polymorphisms have been identified that modulate the risk of suffering devastating health problems associated with smoking, or that can predict which smoking cessation technique would work best for a given individual.<sup>8</sup>

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<sup>7</sup> Thorgeirsson, T. et al. Sequence variants at CHRNA6 and CYP2A6 affect smoking behavior. *Nat Genet.* 42(5):448-53, 2010.

<sup>8</sup> Drgon, T. et al. Genome-wide association for nicotine dependence and smoking cessation success in NIH research volunteers. *Molecular Medicine* 15(1-2):21-27, 2009.

The combined initiatives and projects spearheaded by NIDA are poised to provide new insights into the multifarious genetic and behavioral processes that underlie addiction and substance abuse/use disorders.

#### Item

**Comparative Effectiveness** – The Committee encourages NIDA to continue its investment in comparative effectiveness research so that proven models of drug abuse prevention and treatment can be further refined. (p. 113)

#### Action taken or to be taken

NIDA has been a strong supporter of CER research through our National Drug Abuse Treatment Clinical Trials Network (CTN), as well as through grants and contracts focused on testing and implementing prevention, treatment, and HIV interventions in real world settings. The CTN is a network comprising multiple nodes, or Regional Research and Training Centers (RRTC)s—each linked with several Community-Based Treatment Programs (CTPs). This framework allows the CTN to provide an infrastructure for the rapid, multisite testing and delivery of promising science-based therapies to patients in community-based treatment settings nationwide. The CTN's mission is broader than conducting research, in that it aims to disseminate evidence-based findings rapidly and to train treatment providers in their use to encourage adoption.

NIDA is also supporting CER research in the criminal justice setting, where drug use disorders are over-represented and where, without treatment, offenders remain at high risk for relapse, recidivism, and even overdose upon their return to the community. Thus, NIDA supports an ongoing randomized clinical trial in Baltimore to examine the effectiveness of methadone maintenance treatment (MMT) provided to male prisoners with pre-incarceration heroin addiction. Inmates were randomly assigned to one of three groups: (1) educational counseling only, with passive referral to treatment upon release, (2) counseling in prison with transfer to methadone treatment upon release, and (3) counseling and methadone treatment begun in prison, continuing in a community-based methadone maintenance program upon release. Results show that even 12 months after release, those who received MMT in prison had fewer drug positive urines and increased time in drug treatment. MMT is an inexpensive and effective intervention that can help break the vicious cycle of drug abuse, criminal recidivism, and exposure to infectious diseases, netting huge savings in economic and social costs.

To address the research-to-practice gap for implementing evidence-based prevention programs, NIDA supported a randomized controlled trial of the Communities that Care (CTC) coalition-based prevention system, which identifies community-specific risk and protective factors and implements evidence-based interventions that address them. The CTC prevention system achieved significant reductions in the initiation of alcohol use, tobacco use, binge drinking, and delinquent behavior among middle school youth

as they progressed from the fifth through seventh grades, compared to standard non-tailored community-based prevention.

Finally, NIH invested significant ARRA funds to support CER research projects that include Web-based technologies to improve treatment access, better and safer medications for treating opioid dependence, and more effective treatments for conditions often comorbid with drug abuse, such as pain, HIV, and psychiatric disorders.

#### Item

***Engaging the Medical Community*** - The Committee is pleased with NIDA's initiative designed to reach out to physicians, physicians in training, and other healthcare professionals regarding substance abuse. The Committee also supports NIDA's ongoing efforts around the Centers of Excellence for Physician Information and its Screening, Brief Intervention, and Referral to Treatment initiative. The Committee urges the Institute to continue its focus on activities to provide physicians and other medical professionals with the tools and skills needed to incorporate NIDA-funded research findings into their clinical practices. (p. 113,114)

#### Action taken or to be taken

In April 2009, NIDA launched its first comprehensive Physician's Outreach Initiative, NIDAMED, to assist medical professionals as the first line of defense against substance abuse and addiction. At the heart of NIDAMED is the NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NMASSIST). This web-based interactive tool (adapted from the ASSIST Version 3.0 developed by the World Health Organization) guides clinicians through a series of screening questions for tobacco, alcohol, illicit and prescription drug abuse; and based on the patient's responses, generates a substance involvement score that suggests the level of intervention needed. The NMASSIST tool has been accessed more than 7,000 times since data collection began on September 17, 2009. The weekly access rate is approximately 130 times per week. A number of resources accompany the NMASSIST, including a Clinician's Resource Guide, a Quick Reference Guide, and a Patient Postcard designed to encourage patients to discuss all drug use with their doctors to help ensure proper medical care. In 2010, NIDA adapted the patient postcard into a poster to be displayed in physician offices. In partnership with the Health Resource Services Administration, this poster has now been distributed to more than 26,000 community health centers across the country.

The broad availability of these tools is an important step toward the goal of integrating substance abuse screening, brief intervention, and referral to treatment (SBIRT) into medical care. However, more research is needed on the effectiveness of systems-level models of care that would integrate SBIRT into primary care medical settings. In 2008, NIDA awarded eight grants to address this issue, including studies of SBIRT for opioid dependence in emergency department settings, for emerging adults in primary care, and in comparing computer vs. therapist-delivered brief interventions in primary care. In 2010, NIDA hosted a meeting of these grantees to outline the current state of research

findings, barriers to conducting SBIRT research, strategies to overcome these barriers, and future research needs.

Finally, to help integrate substance abuse and addiction diagnosis, referral, and treatment into standard medical practice, NIDA launched its Centers of Excellence for Physician Information (CoEs) in 2006, specifically targeting physicians in training. In 2009, the first of the CoEs curriculum resources—educational materials to advance medical students' and resident physicians' understanding of drug abuse and addiction—were released. NIDA is continuing to work with the CoEs to disseminate these curriculum resources and develop additional ones.

#### Item

***HIV/AIDS and Criminal Justice Populations*** - The Committee is concerned about drug abuse and HIV/AIDS in criminal justice populations, and it supports research efforts to empirically test the "seek, test, and treat" paradigm. NIDA should continue its initiative in this area, which will yield important linkages to appropriate health services and effective HIV prevention, intervention and treatment in these populations. (p. 114)

#### Action taken or to be taken

In the United States, a million people currently live with HIV, and 50,000 new cases occur each year, a rate that has held steady for the past 10 years. From the time it began, the HIV/AIDS epidemic has been closely linked with drug abuse and addiction. It is a linkage that—over the past 30 years—the National Institute on Drug Abuse (NIDA) has sought to learn more about, both to understand the critical role of drug abuse in the spread of HIV and to learn how best to prevent and treat these intertwined conditions. Indeed, drug abuse treatment *is* HIV prevention, in that it reduces the behaviors that put people at risk.

Individuals involved in the criminal justice system represent a vulnerable population with disproportionately high rates of substance abuse disorders and HIV/AIDS. In fact, 14 percent of HIV-infected individuals pass through the criminal justice system each year. However, this junction also offers opportunity—an avenue by which to provide drug abuse and HIV prevention services and to screen for HIV and start people in treatment, following up in the community post-release and creating a continuum of care. This approach has the potential to not only prevent those who are HIV positive from developing AIDS, but to also reduce the HIV viral load population-wide and, consequently, disease incidence—which has been stubbornly difficult to alter.

In FY10, NIDA and the National Institute of Mental Health (NIMH) funded 12 research grant applications to develop and test strategies for identifying individuals within criminal justice systems who have not recently been tested (seek), provide them with HIV testing (test), and initiate, monitor, and maintain Highly Active Antiretroviral Therapy (HAART—a combination therapy used in treating AIDS and HIV) for those who test positive (treat). This exciting initiative stands not only to expand access to HIV testing for those in the criminal justice system, but to improve the provision and maintenance of HAART in the community following reentry, thereby improving outcomes for those who are HIV

positive. To coordinate this research effort, NIDA sponsored a meeting in November 2010 to harmonize data collection and encourage collaboration between these grantees in addressing major research questions.

HIV prevention services in the criminal justice system also tend to be limited and of diminished quality. In addition, few community agencies specifically target individuals who are part of community correctional programs or who have been released from correctional facilities. Therefore, NIDA continues to support research to increase HIV/AIDS and drug abuse prevention efforts among offender and other under-served populations, specifically targeting women, juvenile offenders, and racial/ethnic minorities disproportionately affected by the HIV epidemic.

Successful results from these initiatives could catalyze a needed paradigm shift in how to conduct HIV prevention and treatment interventions, particularly in populations at heightened risk, many of whom remain largely out of the treatment loop

#### Item

***Medications Development*** - The Committee encourages NIDA to continue to support research to develop new, effective medications that could, either by themselves or combined with validated behavioral therapies, help alleviate the personal and social impact of this complex disease. (p. 114)

#### Action taken or to be taken

The development of addiction medications is a top research priority for NIDA. The reluctance of pharmaceutical companies to invest in this area, largely because of perceived financial disincentives and associated stigma, demands our unflagging commitment—particularly in light of recent pharmaceutical industry trends to reduce investment overall in psychotherapeutic medications.

Recent scientific discoveries, which have revealed the involvement of multiple circuits and neurotransmitters in addiction that go beyond the reward system to affect learning, memory, executive function (e.g., decision-making), and emotional reactivity, are ripe for continued investment. Among the most promising are addiction vaccines, which rely on the body's own immune system to produce antibodies that can neutralize a drug while still in the bloodstream, preventing it from entering the brain. This approach has been used to test a vaccine for cocaine addiction, showing promising results in participants who generated sufficiently high levels of anti-cocaine antibodies in their bloodstreams. Using ARRA funds, NIDA is also supporting development of a vaccine (NicVAX) against tobacco addiction, awarding a \$10 million ARRA grant to Nabi Pharmaceuticals in 2009 to help fund a Phase 3 trial (see Significant Item on "Tobacco Addiction"). Another innovative approach is represented by long-acting (or depot) forms of medications. Vivitrol, for example, is an extended release opioid antagonist that just received FDA approval for treating heroin addiction, based on findings generated in Russia. Because it is a non-narcotic, non-addictive medication administered only once a month, it may help those who prefer not to use other opioid medications (e.g., buprenorphine or methadone) or who do not have access to methadone clinics or the

ability to attend daily treatment. NIDA is supporting research on Vivitrol's effectiveness in other populations, including those in the criminal justice system. In addition, NIDA is funding, through an ARRA GO grant, a randomized controlled trial of a novel formulation of buprenorphine (Probuphine) for opioid addiction, delivered as an implant under the skin and providing continuous drug delivery for 6 months. Previous studies have shown that the implant offers the same benefits as sublingual buprenorphine, while also potentially preventing poor treatment adherence and diversion.

Rapid advances in genetics and related technologies are ushering in the age of personalized medicine, particularly pharmacogenetics, which relates to the influence of genetic variation on drug response. For example, NIDA-supported researchers have identified a genetic variation that may help predict alcoholic patients' response to naltrexone, with similar findings emerging in the treatment of nicotine addiction. Prescribing physicians may thereby be able to improve and individualize patient treatment by taking genetic variation into account.

NIDA is especially interested in pursuing medications for addictions where none yet exist—e.g., stimulants and cannabis. This is reflected in the funding opportunities issued in FY 2010, which included, NIDA's first Translational Avant-Garde Awards for Medications Development Research, resulting in four grants to support novel approaches for treating tobacco and cocaine addiction, including immunotherapy and targeting of the body's own cannabinoid system. Further, recent grantees in NIDA's Medications Development Centers of Excellence program are evaluating medications for cocaine plus alcohol dependence and for stimulant (cocaine and methamphetamine) addiction, using genetic matching for medication response. NIDA also recently funded 12 projects to jumpstart promising medications not quite ready to be tested in large, costly randomized controlled trials, for multiple drugs and abuse-related conditions.

#### Item

***Military Personnel, Veterans, and Their Families*** – The Committee understands that NIDA has joined with the VA and two other NIH Institutes to support research on substance abuse and associated problems among U.S. military personnel, veterans and their families. Many returning military personnel need help confronting a variety of war-related problems including traumatic brain injury, post-traumatic stress disorder, depression, anxiety, sleep disturbances, and substance abuse, including tobacco, alcohol and other drugs. Many of these problems are interconnected and contribute to individual health and family relationship crises, yet there has been little research on how to prevent and treat the unique characteristics of wartime-related substance abuse issues. The Committee commends NIDA for this crucial work and asks for an update in the fiscal year 2012 congressional budget justification. (p.114)

#### Action taken or to be taken

As requested by the Committee to provide an update on military personnel, veterans, and their families, NIDA presents the following. U.S. combat operations in Iraq and Afghanistan have placed tremendous strain on military personnel and their families, with some experiencing devastating consequences, such as mental health disorders and

cognitive impairment..Combat exposure is a key driver of problems such as depression and post-traumatic stress disorder (PTSD). For example, according to research from the ongoing Department of Defense funded Millennium Cohort Study, launched in 2001 and involving both military and civilian researchers, new-onset PTSD symptoms or diagnoses are three-fold greater in soldiers who deployed and were in combat versus those who were not in combat or who did not deploy.<sup>9</sup> Substance use disorders are also of concern in this population. A SAMHSA report revealed that an annual average of 7% of veterans aged 18 or older experienced serious psychological distress, while 7.1% met criteria for a past year substance use disorder, and 1.5% had both.<sup>10</sup>

Indeed, as reported in February 2010 by the White House's Office of National Drug Control Policy (ONDCP), analyses of U.S. Department of Defense surveys among military and active duty military personnel show a sharp uptick in drug abuse. This increase is driven by the nonmedical use of prescription drugs, which soared from 2 percent in 2002 to 11 percent in 2008.<sup>11</sup> In addition to prescription drug abuse, problems with alcohol and nicotine are the most prevalent and pose a significant risk to the health of active, reserve, and guard military personnel.<sup>12</sup>

To better understand the underlying causal factors and to elucidate how best to prevent and treat the interconnected health problems being faced by returning veterans and their families, NIDA has joined forces with NIAAA, NCI, and the Department of Veterans Affairs in a joint call for research entitled "Substance Use and Abuse among U.S. Military Personnel, Veterans and their Families." Eleven research institutions in 11 states will be receiving more than \$6 million in Federal funding to support research directed primarily at substance abuse and related conditions experienced by veterans returning from wars in Iraq and Afghanistan.

Among other topics, proposed studies will examine use and abuse of prescription opioids among combat veterans; treatment integration for the interrelated problems facing returning military personnel, including depression, anxiety, sleep disturbances, and substance abuse; veterans' treatment-seeking patterns (how and why they do or do not seek out treatment); and a Web-based parenting program focused on combat-deployed families' needs to improve parenting and child adjustment, and reduce youth substance use risk. Resulting research should help identify risk and protective factors, develop and test targeted substance abuse prevention and treatment interventions,

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<sup>9</sup> Smith TC et al. for the Millennium Cohort Study Team. New onset and persistent symptoms of posttraumatic stress disorder self-reported after deployment and combat exposures: prospective population-based U.S. military cohort study. *British Medical Journal* 336(7640):366-71, 2008.

<sup>10</sup> [www.oas.samhsa.gov/2k7/veteransDual/veteransDual.htm](http://www.oas.samhsa.gov/2k7/veteransDual/veteransDual.htm)

<sup>11</sup> Bray et al. Substance use and mental health trends among U.S. military active duty personnel: key findings from the 2008 DoD health behavior survey. *Military Medicine* 175(6):390-99, 2010.

<sup>12</sup> [www.millenniumcohort.org](http://www.millenniumcohort.org)

and explore the utility of existing evidence-based prevention interventions and services for substance abuse—alone or with comorbid conditions—across the deployment cycle for military personnel, veterans, and their families.

Item

***Pulmonary Hypertension*** - The Committee commends NIDA for its interest in pulmonary hypertension related to methamphetamine abuse and requests an update in the fiscal year 2012 congressional budget justification on efforts to initiate a large scale survey to assess the frequency of pulmonary hypertension in methamphetamine users. (p. 114)

Action taken or to be taken

Earlier this decade, national surveys showed a stabilization or decline in methamphetamine abuse in the United States, especially among young people. However, data from the 2009 National Survey on Drug Use and Health showed a significant increase between 2008 and 2009. NIDA recognizes the myriad problems this drug poses and continues to support actively a comprehensive research portfolio that aims to understand how methamphetamine affects the brain and body and to develop effective prevention and treatment interventions.

NIDA-supported research has shown that methamphetamine abuse can lead to cardiovascular problems, such as rapid and irregular heartbeat, increased blood pressure, and stroke. A study published in 2006 showed that patients with pulmonary arterial hypertension of unknown origin were 10 times more likely to have used stimulants (including methamphetamine) than patients with pulmonary hypertension and known risk factors. However, no large scale surveys on the frequency of pulmonary hypertension in methamphetamine abusers have been conducted.

To encourage research on the prevalence of drug abuse and its consequences across different population groups, NIDA has an ongoing program announcement (PA) titled “Epidemiology of Drug Abuse,” released in March 2008 and set to expire in May 2011. Any highly meritorious applications examining the frequency of pulmonary hypertension among methamphetamine abusers received in response to this announcement would be considered for funding. Current grantees include those conducting studies on the health effects of homemade amphetamine-like drugs in the Ukraine (where entwined injection drug use and HIV occur at epidemic proportions) and research on the social dynamics of a local methamphetamine market to discover through descriptive ethnographic and quantitative longitudinal data how risk behaviors and their consequences, including health effects, are influenced by the markets in which users acquire drugs. The PA encourages researchers to examine the medical consequences of drugs of abuse and to incorporate innovations in epidemiologic study design, including use of contemporary longitudinal analyses.

Item

***Relapse Prevention*** – The Committee applauds NIDA for supporting emerging research on the use of cognitive-enhancing therapy to reduce drug abuse relapse. The

Committee understands that this research is currently conducted with animal models, and it encourages NIDA to support research that tests this model in clinical populations. (p. 114)

#### Action taken or to be taken

NIDA will continue to support research that leads to more effective strategies for preventing relapse to drug use. A growing body of research suggests that the functional enhancement of specific cognitive domains that are weakened by the addiction process has the potential for counteracting the power of relapse triggers, thus improving treatment efficacy. Most of this research has been done in animals, where the impact of drugs and pharmaceutical agents on brain circuitry can be evaluated directly. For example, preclinical studies suggest that medications enhancing cholinergic neurotransmission may attenuate marijuana-induced cognitive impairments<sup>13</sup> and that d-cycloserine (a partial glutamate NMDA agonist) can facilitate extinction of cocaine<sup>14</sup> and alcohol<sup>15</sup> seeking in animal models of addiction. NIDA is committed to extending this research into the clinical domain. Research areas of interest include:

- *Stimulant addiction*- Cocaine and methamphetamine abusers display significant cognitive impairments, especially in attention, working memory, and inhibitory control functions, which seem to predict poor treatment retention and outcome. Preliminary results indicate that existing medications that target acetylcholine and norepinephrine and that have low abuse potential may enhance cognitive function in stimulant users.
- *Marijuana addiction*. Abstinence rates following behavioral therapies for marijuana addiction are modest at best. Exposure to marijuana is associated with dose-related cognitive impairments in attention, working memory, verbal learning, and memory functions, which may not be completely reversed upon cessation of marijuana use. Therefore, targeting these cognitive impairments may be a promising strategy for the treatment of marijuana addiction.
- *Nicotine*. There is increasing evidence that attenuating conditioned reactivity to smoking cues may aid abstinence of smoking and prevention of smoking relapse in individuals with nicotine dependence. Accordingly, NIDA is interested in further evaluating the therapeutic potential of d-cycloserine, which in a pilot investigation attenuated reactivity to smoking cues in nicotine dependent smokers.

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<sup>13</sup> Mishima, K., Egashira, N., Matsumoto, Y., Iwasaki, K., & Fujiwara, M. Involvement of reduced acetylcholine release in  $\Delta 9$  THC-induced impairment of spatial memory in the 8-arm radial maze. *Life Sciences*, 72, 397–407, 2002.

<sup>14</sup> Thanos PK, Bermeo C, Wang GJ, Volkow ND. D-cycloserine accelerates the extinction of cocaine-induced conditioned place preference in C57bL/c mice. *Behav Brain Res*. 199(2):345-9, 2009.

<sup>15</sup> Vengeliene V, Kiefer F, Spanagel R. D-cycloserine facilitates extinction of conditioned alcohol-seeking behavior in rats. *Alcohol* 43(6):626-9, 2008.

NIDA will continue to support basic and clinical research to explore the usefulness of pharmacological and/or behavioral cognitive enhancement as a means to improve treatment retention and outcomes. Evidence of this commitment is the support of six grant applications in response to a funding announcement titled “Cognitive Remediation Approaches to Improve Drug Abuse Treatment Outcomes.”

#### Item

***Teens and Drug Abuse*** - The Committee commends NIDA for its educational efforts to raise awareness among teens regarding the harmful health effects associated with drugs of abuse. (p. 114)

#### Action taken or to be taken

NIDA recognizes the critical role of communicating with teens about the negative health effects of abusing drugs, including addiction, to which they are more vulnerable because of the still-developing state of their brain and their higher rates of drug experimentation. NIDA uses an array of communication platforms to reach teens with accurate scientific information about drug abuse to help them make healthy decisions. *Traditional media.* NIDA’s “After the Party” PSAs, spun off a previous campaign to inform teens about the link between drug abuse and HIV, aired more than 25,000 times between 9/2007 and 5/2009. This translates into nearly \$4.4 million in free media time garnering almost 2.4 million media impressions (estimated viewers for the time slots in which the PSAs aired).

*Web-based.* NIDA’s teen website features videos and a new teen blog called the Sara Bellum Blog (SBB), an innovative effort to meet teens where they “live” and to share with them science-based messages about health. SBB emphasizes personal responsibility and encourages readers to share what they have learned within their peer networks. During November 2010, the blog had 14,000 unique visits and 150,000 page views. In spite of its recent launch, SBB has been recognized through several awards in 2010, including PR News; Digital PR Awards; Honorable Mention Juggle.com; Top Blog, Government; NIH Plain Language Award; Wellsphere People’s Health Blogger Awards; and Best 100 Winner in 2009.

Another extraordinary event is NIDA’s annual Drug Facts Chat Day, in which NIDA scientists answer teen questions about drugs and their impact on the brain and body. Last year, experts answered more than 1,200 questions from students across the Nation. This effort will be expanded in 2010 with the launching of National Drug Facts Week, which will encourage communities to hold local events to shatter myths about drug abuse.

*Institutional Partnership-* NIDA has introduced a special Addiction Science Award at the Intel International Science and Engineering Fair, with impressive results. For example, one of the first cycle awardees was recruited by a Harvard media lab this year to further analyze and publish his data on teenage video game addiction, and the 2010 first prize winner carried out a remarkable project, entitled “Computer modeling to identify new medications for nicotine addiction”. NIDA also continues its partnership with Scholastic

magazine, which is sent out quarterly to thousands of young students across the country to convey to them the consequences of drug abuse.

*Neuromarketing research*- NIDA supports the exploration of new campaign strategies, such as interactive web-based technologies and the use of brain imaging, to maximize the effectiveness of our prevention messages<sup>16</sup>. The latter approach is exemplified by an exciting recent study suggesting that the innovative use of imaging technologies could help us craft better messages by delineating which prevention messages resonate with which target audiences and whether that translates into more healthful behaviors.

#### Item

**Tobacco Addiction** - The Committee applauds the recent progress of NIDA-supported researchers toward identifying genetic factors that contribute to nicotine dependence and affect the efficacy of smoking cessation treatments, and it urges NIDA to continue developing much-needed evidence-based treatments, medications, and prevention strategies to combat nicotine addiction. (p. 114)

#### Action taken or to be taken

Tobacco use is the leading preventable cause of disease, disability, and death in the United States, resulting in more than 440,000 deaths each year—nearly one in every five deaths—mainly caused by cancer, respiratory diseases, and cardiovascular disease. While public health interventions and advances in behavioral and pharmacological treatments have inspired dramatic reductions in the initiation of tobacco use and in the prevalence of tobacco-related disease and death, approximately 71 million Americans report being current tobacco users. In response to this alarming rate of continued use, NIDA supports a comprehensive research portfolio aimed at understanding nicotine's effects on the brain and body, developing effective prevention strategies and developing new medications to help addicted individuals quit for good.

NIDA is working with the pharmaceutical industry to translate pioneering findings into treatments for smokers. An example is an anti-nicotine vaccine, known as NicVAX, designed to promote tobacco cessation and prevent relapse. Using ARRA funds, NIDA awarded a \$10-million dollar grant to Nabi Biopharmaceuticals in 2009 to conduct a Phase III clinical trial. NicVAX uses an immunotherapy approach, generating antibodies that bind to nicotine molecules while they are still in the bloodstream, thus preventing the drug from entering the brain and exerting its rewarding effects. If successful, NicVAX is poised to be the first-in-class vaccine for smoking cessation. As a result of ARRA funding, Nabi entered an agreement with GlaxoSmithKline to provide an additional \$40 million to exclusively in-license NicVAX on a worldwide basis and

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<sup>16</sup> Langleben DD, Loughead JW, Ruparel K, Hakun JG, Busch-Winokur S, Holloway MB, Strasser AA, Cappella JN, Lerman C. Reduced prefrontal and temporal processing and recall of high "sensation value" ads. *Neuroimage*. 46(1):219-25, 2009.

develop follow-on, next-generation nicotine vaccines. This work is an excellent example of leveraging government resources to further develop and market a medication for tobacco addiction.

NIDA is also supporting research on other medications. For example, Embera NeuroTherapeutics recently received a grant to advance the development of a new combination drug that targets multiple brain systems to promote tobacco cessation and maintain abstinence; and through our new Avant-Garde award for medications development, NIDA is supporting a novel approach targeting the endogenous cannabinoid system. Studies using animal models of relapse have shown that blocking the enzyme that degrades cannabinoids reduces nicotine self-administration and prevents nicotine-induced reinstatement.

Additional funding opportunity announcements aim to promote new discovery of medications to combat nicotine addiction, while at the same time NIDA is initiating a product development partnership (PDP) that would involve public (government agencies and institutes), non-profit (academia, NGOs, philanthropic institutions), and private sector entities to accelerate the development and production of smoking cessation drugs at a reasonable cost.

NIDA is also continuing to support research identifying genetic variations that not only affect susceptibility to tobacco addiction, withdrawal, and relapse, but also influence quit success. The application of these findings will lead to the earlier identification of those most at risk as well as specialized treatment strategies that can be individually tailored to meet the needs of smokers.

To expand access to various smoking cessation behavioral interventions and increase treatment options, NIDA is supporting research on alternative delivery formats, such as those using web, PDA, or testing-based approaches.

## National Institute on Alcohol Abuse and Alcoholism (NIAAA)

### Senate Significant Items

#### Item

***Collaboration With State Substance Abuse Agencies*** - The Committee applauds the NIAAA for working with State substance abuse agencies and encourages collaborative initiatives to ensure that research findings are relevant and adaptable by publicly funded State substance abuse systems. (p. 113)

#### Action taken or to be taken

NIAAA values the opportunity to put research into practice. Through collaborations with the Substance Abuse and Mental Health Services Administration (SAMHSA), NIAAA helps ensure that science informs both policy and practice in SAMHSA-funded programs which are available to state substance use agency directors and others. For example, NIAAA collaborated with SAMHSA on its most recent underage drinking prevention ad campaign for parents, providing detailed input on the development and content of the accompanying web site as well as other aspects of the campaign. The Acting Director of NIAAA serves on the Expert Panel of SAMHSA's Fetal Alcohol Spectrum Disorders Center of Excellence. Through the auspices of this group, the Acting Director, NIAAA advises the FASD coordinators within the State government substance abuse agencies on matters related to treatment and prevention interventions for both alcohol use during pregnancy and FASD. NIAAA senior staff serve on SAMHSA's advisory committee for the Strategic Prevention Framework State Incentive Grant (SPF-SIG) community program evaluation as well as committees to evaluate ways to improve state and community level alcohol surveillance data.

To encourage dialog between NIAAA and State substance abuse agencies, NIAAA's Acting Director as well as senior staff present at the annual conferences of the National Prevention Network (which includes state substance abuse agency directors) and the Community Anti-Drug Coalitions of America (CADCA) among others. These presentations showcase research findings on effective prevention programs and interventions, and create an opportunity for states to discuss how future research can help them better meet their program needs.

#### Item

***Comorbidity*** - The Committee recognizes that information from NIAAA's National Epidemiologic Survey of Alcohol Related Conditions and the National Longitudinal Alcohol Epidemiologic Survey has transformed our understanding of alcohol use disorders in the U.S. population at large. These unique resources have provided important information on the extent and nature of alcohol use disorders and their relationship to other substance use problems and co-occurring mental disorders. (p.113)

#### Action taken or to be taken

NIAAA continues to support research that mines the vast data resources made possible by the two waves of the National Epidemiologic Survey of Alcohol Related Conditions (NESARC) and the earlier National Longitudinal Alcohol Epidemiologic Survey (NLAES). These surveys provide comprehensive, detailed data on alcohol consumption, use of tobacco and other drugs, symptoms of alcohol and specific drug use disorders, psychological disorders (e.g., mood, anxiety, personality) and other potential risk factors (e.g., childhood abuse, posttraumatic stress disorder, attention deficit-hyperactivity disorder). Current analyses of the NESARC data include dimensionality studies on alcohol and drug use disorders to support changes in the American Psychiatric Association diagnoses for substance use disorders. Studies on the co-morbidity of alcohol and drug use disorders and post traumatic stress disorders, anxiety disorders and mood disorders are also underway.

Moving forward, in 2012 NIAAA will initiate NESARC-III, which will survey a new cohort of over 45,000 individuals across the U.S. DNA samples will be collected from survey respondents for the purpose of gene sequencing, thereby adding valuable genetic information to this important database on alcohol and other substance use problems, and co-occurring mental disorders. In addition, new interview data on eating disorders (anorexia nervosa and binge eating disorder), obsessive-compulsive disorder, risky behaviors (needle sharing and condom use), HIV status, and more extensive information on alcohol, drug and mental health treatment will be collected.

## National Institute of Biomedical Imaging and Bioengineering (NIBIB)

### Senate Significant Item

#### Item

**Bone Disease** - The Committee encourages research on bone diseases and disorders utilizing bone imaging. The Committee further encourages the Institute to use engineering strategies to replace and regenerate bone and soft tissue affected by trauma. (p. 115)

#### Action taken or to be taken

Advances in imaging technologies supported by NIBIB can significantly improve the diagnosis and treatment of bone disease. Osteoarthritis (OA) is a common, debilitating disorder without an effective therapy. Magnetic resonance imaging (MRI) is an accurate non-invasive method of assessing early disease changes caused by osteoarthritis. For example, NIBIB-supported researchers are able to show altered collagen structure by MRI that may indicate joint injury or disease. Current routine OA imaging methods only show the late changes of the disease after irreversible tissue loss has occurred. The techniques developed at NIBIB will allow investigators and clinicians to track progress of the disease before tissue loss has occurred, enabling better treatment of joint injuries, faster drug discovery, and improved scientific understanding of OA progression.

Increased image resolution will enable the detection and measurement of bone loss associated with many bone diseases. Specifically, improvements in technologies such as computed tomography (CT) and other techniques that incorporate x-ray imaging will enable better understanding of the pathogenesis and treatment of bone disease. An example of this is a project supported by NIBIB that has developed an X-ray microscope at the Stanford Synchrotron Radiation Light source, which produces 3-dimensional bone images with an unprecedented resolution of 30-40 nanometers and also quantifies the density of bone tissue. It uses two imaging techniques called phase contrast and absorption contrast imaging, and has been tested on mouse cancellous bone. It can display both the structure of bone (such as trabeculae struts), and mineral content and density. The 3-dimensional imaging and characterization of bone nanostructure could be important predictors of bone material properties that cannot be explained by macro or microstructure. This device could be used in the future for visualization and quantification of micro-structural changes in bone resulting from osteoporosis, dental disease, and other pathologies.

NIBIB has taken the lead in research on new and enabling technologies for bone regeneration. Strategies are especially needed for segmental defects - gaps in the bone that are too large to heal via repair mechanisms innate to the individual. NIBIB-supported investigators are developing innovative approaches including, for example: generating scaffolds that are biocompatible, but have the strength and resilience of the native tissue and can be weight-bearing very quickly after transplantation into the

damaged site; formulating drugs that accelerate bone formation and can be incorporated directly into the implant; creating local environments to attract the body's engines of repair – bone stem and precursor cells; and, developing matrices with on-board imaging and sensing capabilities so that healing can be continuously monitored. NIBIB co-sponsored, along with NIAMS and NIDCR, a workshop at the Tissue Engineering & Regenerative Medicine International Society (TERMIS) meeting held in December 2010. The workshop addressed specific areas including: scaffolds, cells, biomolecules, angiogenesis, host responses such as inflammation, and biomechanical conditioning. The meeting will be summarized with the publication of a seminal review of the state-of-the-art in bone regenerative medicine.

## National Center for Research Resources (NCRR)

### Senate Significant Items

#### Item

***Chimpanzee Breeding*** - The Committee is aware that the NCRR instituted a breeding moratorium on chimpanzees that it owns and supports in 1995, and that in 2007 it reaffirmed that moratorium by declaring, "NCRR has determined that it does not have the financial resources to support the breeding of chimpanzees that are owned or supported by NCRR." Nevertheless, disturbing questions have been raised about whether this moratorium is being followed at the New Iberia Research Center [NIRC], which is supported by the NCRR and maintains a mix of chimpanzees that are federally owned and privately owned. Records provided by the NIRC to animal rights groups suggest that in the case of as many as 123 infant chimpanzees born at the NIRC since 2000, either the dam or the sire, or both, were federally owned. The Committee asks the NCRR to investigate this matter promptly, take all steps necessary to ensure that the NIRC is complying with the moratorium, and update the Committee on the results. (p.116)

#### Action taken or to be taken

In response to NCRR's moratorium on the breeding of NCRR-owned chimpanzees, the New Iberia Research Center (NIRC) implemented the following practices:

- Maintain groups of males and females in separate housing arrangements, where possible. NIRC requested, and received, funding from NIH to accommodate the need for additional space to establish all male and all female social groups, and all chimpanzee housing was completed and subsequently occupied in 2006.
- Incorporate the use of Norplant and Intrauterine Devices (IUDs) as a form of contraceptives in female chimpanzees. Norplant was used for four to five years until it was removed from the market.
- Vasectomize specific male chimpanzees, based on input from veterinarians and behavior specialists.

Because the implementation and impact of these practices took time, there were 15 chimpanzee births between 1995 and 1996. Since 1996, there have been 13 accidental births among a total of 70 female chimpanzees. These accidental births resulted from implant failure, relocation of males and females to allow for renovation, and when young animals became prematurely sexually active (prior to an age when birth control measures normally would be administered).

In response to the Committee's concerns, NCRR has confirmed that NIRC does not have an active breeding program involving federally-owned chimpanzees and that the facility is committed to honoring the NCRR moratorium. NCRR has records from NIRC

(which are the same records provided by NIRC in response to an inquiry from the Humane Society of the United States) that indicate that only the 28 births described above (15 +13) have occurred since 1995. NCRR is not sure how the number 123 was arrived at but would be willing to evaluate any additional records that were obtained by other animal rights groups and follow up with NIRC if there are any discrepancies. NCRR has also clarified with NIRC that the chimpanzees that were born after the moratorium went into effect are currently owned and supported by the University of Louisiana at Lafayette. By acceptance of ownership of any newborns, NIRC is in compliance with the conditions of the breeding moratorium as defined in its notification of grant award. NCRR continues to stress the importance of taking all practical measures to minimize the possibility of a pregnancy occurring in NCRR-owned animals.

#### Item

**Human Tissue Supply** - The Committee remains committed to matching the increased needs of NIH-funded researchers who rely upon human tissues and organs to study human diseases and search for cures. Therefore, the Committee encourages the NCRR to increase its core support for its nationwide human tissue and organ procurement network and urge other Institutes to expand their support as well. (p. 116)

#### Action taken or to be taken

The National Disease Research Interchange (NDRI) is one of many nonprofit organizations in the United States that provide human tissue and organ specimens to biomedical researchers for basic and clinical research. The National Center for Research Resources (NCRR) is the lead Institute/Center for the cooperative agreement that funds the Human Tissue and Organ Resource (HTOR), which is a division of NDRI. Since 1995 to the latest statistics, over 73,621 normal and diseased tissues and organ specimens have been shipped by HTOR to biomedical researchers to study diseases such as Alzheimer's, Crohn's Disease, cystic fibrosis, diabetes, glaucoma, heart disease, HIV-AIDS, malaria, multiple sclerosis, and Parkinson's. There were 574 active biomedical researchers utilizing this program this past year, including those that are NIH-funded.

NCRR maintains the core funding for the HTOR cooperative agreement, now in its twentieth year, with co-funding from NEI, NHLBI, NIAID, NIAMS, NIDDK and the Office of Rare Diseases. The NIH Office of Rare Diseases provided additional funding over the past years to support the NDRI Rare Disease Initiative for tissue distribution, research recruitment, source and database development, and outreach to rare diseases patient advocacy groups and their members.

The NDRI and other NIH-funded sources of tissue are instrumental in providing tissue and organ resources to researchers. In addition to NCRR, other NIH Institutes provide funds for mission-specific resources and ways to improve the collection, storage, and distribution of tissues. For example, NCI is developing a national, standardized human biospecimen resource called the cancer Human Biobank (caHUB) and has established a Biospecimen Research Network to systematically address the impact of specific variables in individual specimen types on molecular data from given analysis platforms.

These efforts should help ensure that high quality specimens and associated data are available to study human diseases and develop markers for diagnosis and disease progression as well as effective treatments.

Item

***Research Centers in Minority Institutions (RCMI)*** - The Committee continues to support the RCMI program and encourages the NCRR to strengthen participation from the minority health professions schools. (p. 116)

Action taken or to be taken

In FY 2010, eighteen institutions received funding through the Research Centers in Minority Institutions (RCMI) program and minority health professional schools are well represented in this cohort. Eight medical schools, three schools of pharmacy and one school of veterinary medicine received funding to support a wide array of research resources, ranging from laboratory instruments to out-patient clinical research facilities, to support biomedical research. In FY 2010, NCRR funded RCMI Infrastructure for Clinical and Translational Research (RCTR) awards at two additional health professional schools, bringing the total number of health professional schools receiving funding from this type of award to five. RCTR awards develop institutional research infrastructure to enhance training and career development activities, and accelerate the process of translating research advances to improved health outcomes, especially in minority communities. Research supported by the RCMI program spans a broad range of areas including cardiovascular disease, obesity, cancer, diabetes, women's health, health disparities and neurological diseases.

## National Institute on Minority Health and Health Disparities (NIMHD)

### Senate Significant Items

#### Item

**Urban-based Network** - The Committee encourages the Institute to support a new network of urban-based academic institutions focused on, and with demonstrated commitment and capacity to, addressing recruitment and training needs of minority and urban underserved populations and reducing health disparities in these urban communities. (p. 117)

#### Action taken or to be taken

The National Institute on Minority Health and Health Disparities (NIMHD) program portfolio demonstrates its commitment to the recruitment and training of minorities and underserved populations. The congressionally mandated Centers of Excellence (COE) program is one example of NIMHD programs that promotes partnerships and supports academic institutions many of which are in urban areas. As required by statute, all NIMHD COEs are based at colleges and universities. The COE was created to develop novel programs to make significant advances in reducing and ultimately eliminating health disparities. Health disparities research, as well as the recruitment and training of minorities and underserved populations are an integral part of each COE's program.

COEs located in urban areas have been partnering to address health disparities for several years. For example, New York State's six COEs have collaborated to hold conferences addressing health disparities. Conference themes have included "Overcoming Health Disparities: the Changing Landscape," and "Assuring Equity through Health and Healthcare Reform." Each conference has brought together regional and national experts to discuss workforce training, the health professions pipeline, health disparities research and other related topics.

Another example of collaboration in an urban area between an NIMHD COE and another university is provided by a research partnership formed by the University of South Carolina's Institute for Partnerships to Eliminate Health Disparities and Claflin University, an HBCU. The collaborative effort, the "Coordinating Center of Excellence in Social Promotion of Health Equity Research" was created for the express purpose of recruiting, training and mentoring students, faculty, and future research leaders wishing to conduct work in minority health and health disparities. The target population of the Coordinating Center includes minorities in urban South Carolina.

The NIMHD will continue to support programs that promote partnerships to address the recruitment and training of minorities and underserved populations in urban communities. In addition, it will continue to encourage applications from academic institutions in urban areas in response to its Funding Opportunity Announcements.

## Fogarty International Center (FIC)

### Senate Significant Items

#### Item

***Global Health Research Training and Workforce Capacity*** - The Committee believes that the U.S. effort to improve health in the developing world can only succeed if other countries can contribute the necessary expertise and knowledge to fight malaria, neglected tropical diseases, and other infectious diseases that disproportionately impact the global poor. The FIC plays a strong role by supporting long-term research and training partnerships between U.S. research institutions and those in developing countries. The Committee supports the FIC's continued work in this area. (p.117)

#### Action taken or to be taken

One of Fogarty's goals in its Strategic Plan FY 2008-FY 2012 is to develop human capital to meet global health challenges. Fogarty will continue to support strengthening research capacity in low- and middle-income countries to address the global burden of infectious diseases. Research training will remain a high priority, and Fogarty will continue to invest two-thirds of its budget in building research capacity related to both infectious and non-communicable diseases.

Fogarty's Global Infectious Diseases Research Training Program addresses research training needs related to infectious diseases that are endemic in developing countries. For example, in FY 2010, Fogarty awarded a new five-year research training grant that builds on a two decade old partnership between the University of California San Francisco and Makerere University. These institutions will work to strengthen scientific capacity in Uganda and provide hands-on training opportunities for junior scientists, including clinical trials of new anti-malarial drug candidates.

The International Implementation, Clinical, Operational and Health Services Research Training Award for AIDS and Tuberculosis (TB) supports strengthening the capacity of foreign institutions to conduct clinical and implementation research focused on HIV, TB, and HIV/TB co-infection prevention and treatment. For example, a recent Fogarty award is enabling Brazilian investigators to obtain research training in operational and health services research related to TB. This award will build on a 15-year partnership between the Johns Hopkins University and the Federal University of Rio de Janeiro, and the result will be a new cadre of researchers who can make substantial contributions to TB control both in Brazil and globally.

Understanding the role of environmental risk factors will be critical to successfully confront some infectious diseases. With support from a research training grant awarded under Fogarty's International Training and Research Program in Environmental and Occupational Health (sponsored in part by the National Institute of Environmental Health Sciences), scientists at the University of California at Berkeley

and Sri Ramachandra University in Chennai, India are collaborating to study indoor air pollution and its impact on the incidence of tuberculosis.

Fogarty-sponsored trainees often contribute to major scientific advances. For example, the first results from a large clinical trial using candidate microbicides that use anti-retrovirals (ARVs) found that the incorporation of an ARV into a vaginal gel was more than 50 percent protective against HIV infection, when used as directed. This finding is an important step toward empowering an at-risk population with a safe and effective HIV prevention tool. Notably, six of the authors on this study are current or former Fogarty-sponsored trainees. The lead scientists on this study also explicitly recognized Fogarty's training support in making the trial possible.

FIC also is administering a major new initiative called the Medical Education Partnership Initiative (MEPI) – a joint effort of the Office of the Global AIDS Coordinator, the Health Resources and Services Administration, the Department of Defense, the U.S. Agency for International Development, the Centers for Disease Control, and 17 NIH Institutes and Centers. MEPI supports institutions in Sub-Saharan African countries that receive PEPFAR support and their U.S. partners to develop new models of medical education and to strengthen the capacity of medical students and faculty to conduct multidisciplinary locally driven research that responds to the health needs of their countries. Notably, over half of the MEPI grants have been awarded to long-standing academic partnerships that have been supported by Fogarty for over ten years.

## National Library of Medicine (NLM)

### Senate Significant Items

#### Item

**Access to Research Information-** The Committee applauds the NLM and the Nation's medical librarians for their continuing efforts to improve public access to biomedical information, and it encourages the NLM to continue to work with the network of medical libraries to ensure rapid access to valuable health information. (p. 118)

#### Action taken or to be taken

NLM encourages access to health information via the over 5,600 health sciences libraries that comprise the National Network of Libraries of Medicine (NN/LM). The mission of the NN/LM is to provide equal access to biomedical information to all U.S. health professionals and the public. The NN/LM facilitates this access by providing training, awareness and funding opportunities for Network Members to reach these populations; and by connecting health professionals and consumers to libraries that will provide services to them. NLM coordinates the Network through five year competitive contracts with eight institutions that serve as Regional Medical Libraries (RML). The competition for the 2011-2016 NN/LM Contracts is currently underway, with awards to be announced May 1, 2011. The new awards will continue a focus on improving access to valuable health information and developing and enhancing collaborative partnerships with Network libraries, state library agencies, state, public and school libraries, public health departments, community-based organizations (CBOs), and other regional, state, and local organizations that provide health information to the public. The new NN/LM contracts will also work to develop collaborations with the DHHS regional extension centers (RECs).

The NN/LM continues to provide funding to Network Members to conduct special projects to reach health professionals, the public health workforce, consumers and minority and underserved populations. More than 1,100 outreach projects have been supported by the NN/LM during the current contract with an average of 270 projects per contract year to date. Examples include:

- The Marshall Medical Center Health Library in Placerville, CA conducted an information outreach campaign to reach community physicians, rural health clinics, community support groups, public librarians, public health nurses and senior services groups in El Dorado County.
- The Hardin Library for the Health Sciences at the University of Iowa improved access to consumer health information in four of Iowa's most diverse and disparate communities by placing computers in four community clinics.
- The Families Helping Families of Northwest Louisiana conducted a project to improve access to electronic consumer health information for consumers,

underserved and minority health care professionals, public health workers, public libraries and community-based and faith-based organizations.

- The Three Rivers AHEC in Columbus, GA used the statewide Distance Learning Network to conduct educational programs on the mental health issues of Post Traumatic Stress Disorders (PTSD) and mild Traumatic Brain Injuries and their effects on soldiers and their families.

The NN/LM continues its efforts to increase public access to health information by requiring that all NN/LM funding announcements for special projects include a the stipulation that any publications resulting from the NN/LM funding must be submitted to PubMed Central. PubMed Central is also promoted throughout the NN/LM as a free digital archive of biomedical and life sciences journal literature.

#### Item

***Disaster Information Management*** - The Committee encourages NLM's continued efforts to identify and implement best practices for providing information during disasters, develop innovative products and services to serve emergency responders and preparedness activities, and conduct research to support disaster health information management and recovery efforts. The Committee also encourages the NLM to make accessible the broad range of literature on disaster health, including an information portal for traumatic brain injury and post traumatic stress disorders. (p. 118)

#### Action taken or to be taken

NLM has made significant progress in developing tools and providing access to disaster health information for all phases of disasters including mitigation, preparedness, response, and recovery. Several resources assist emergency responders and first receivers in responding to hazardous materials (HazMat) incidents or possible terrorist incidents involving chemical, biological or radiological agents. In keeping up with new technologies, new apps for the iPhone/iPod touch have been developed for these resources and versions for other mobile platforms are under development.

NLM continues to work locally with the National Naval Medical Center, Suburban Hospital/Johns Hopkins Medicine and the NIH Clinical Center through the Bethesda Emergency Preparedness Partnership to explore new methods to improve patient management and tracking, develop redundant communications systems, provide access to information, and educate emergency personnel using innovative techniques such as the use of virtual worlds for training and exercises. This partnership is intended to serve as a model that can be used to structure coordination and collaboration among hospitals in communities across the country and to develop innovative tools and approaches that can be deployed elsewhere. For example, following the earthquake in Haiti, NLM expanded the Lost Person Finder concept it developed for use in the Partnership to an iPhone app, ReUnite, that would enable disaster relief workers to report the location of displaced and/or injured persons to an interactive web-based notification wall.

NLM has also developed resources on specific disaster topics and events to assist in situational awareness, response, and long-term recovery from disasters. For example, NLM was the first federal agency to create a Web resource on the health effects of the Gulf oil spill. This information was vital to other government agencies involved in the response as well as workers involved in the clean-up.

The disaster health literature is being organized by NLM via PubMed and the Resource Guide for Public Health Preparedness. New features to improve functionality, usability, and content of the Resource Guide for Public Health Preparedness to improve access to information not readily found in the peer-reviewed scientific literature, but of vital importance to emergency personnel. Guidelines, disaster plans, federal, state, and local government reports, assessments, after-action reports and lessons learned are included in the Resource Guide for easy access by medical and public health workers.

NLM continues to develop a portal on post traumatic stress disorder and traumatic brain injury and includes information on mental health issues in many of its existing resources.

NLM collaborates with numerous government and non-governmental organizations in the development of its disaster health tools and resources to ensure access to high-quality, timely information.

#### Item

**Funding Needs-** The Committee is concerned that NLM funding of extramural research and training programs has declined precipitously, to the point where research opportunities across the full range of biomedical informatics are being deferred, and the necessary cadre of trained informatics scientists and innovators is lacking. The Committee encourages the NLM to contract with the National Research Council of the National Academies of Science to provide: (1) an assessment of the extramural biomedical informatics training programs supported by the funding trends and the career paths of graduates; (2) an assessment of both current and past biomedical informatics extramural research activities funded by the NLM; (3) an assessment of the funding available for extramural biomedical informatics research and education, including trends over time; (4) the identification of promising research opportunities that are not represented in the current NLM portfolio; and (5) an estimate of funding needed to support additional opportunities in biomedical informatics research and education programs, including recommendations on such funding goals as the field evolves further over the next decade. (p.118)

#### Action taken or to be taken

The National Library of Medicine funds scientific research and research training in the field of biomedical informatics, which looks at how computers can best be used to capture, organize, analyze, represent and disseminate biomedical data, information and knowledge. NLM grants led to early advances in areas such as natural language processing of biomedical text, bio-surveillance for health outbreaks, decision support for physicians, and electronic health records. For more than three decades, NLM has been

the primary source of federal training support for research training in biomedical informatics, and currently supports more than 240 informatics trainees each year. Many of today's health IT leaders and outstanding informatics researchers received post-graduate training in NLM-funded informatics training programs.

Although NLM used ARRA funding to increase support for informatics research and to support additional informatics trainees in 2009 and 2010, NLM's allocation of appropriated funds to informatics research has decreased over a period of years. Elimination of some NLM resource grant programs and reduction in funding for informatics research were necessary to preserve stable support for informatics training and for NLM's heavily used information services for researchers, health professionals, and the public.

In the past five years, informatics research has blossomed within many fields of interest to NIH, including genome-wide studies, secondary use of primary health data for research purposes, multi-scale biological modeling, environment, and health. Also, other agencies such as NSF and DARPA have begun funding informatics research. In light of the expanding set of biomedical informatics research questions and new potential sources for funding, it is an opportune time for a study of extramural support for biomedical informatics research and training by a respected outside organization such as the National Research Council, National Academy of Sciences (NAS). NLM has had a productive relationship with NAS over the years that has produced reports of great value such as "For the Record: Protecting Electronic Health Information," "Networking Health: Prescriptions for the Internet" and the recent "Computational Technology for Effective Health Care: Immediate Steps and Strategic Directions." As additional resources become available, NLM would consider commissioning an NAS study of the historical patterns of biomedical informatics research funding, funds and directions of research training for biomedical informatics, promising research opportunities in biomedical informatics, and workforce needs relating to biomedical informatics over the next decade.

#### Item

**Public Access** - In a related matter, NLM international partners are now depositing their manuscripts in PubMed Central, enhancing the benefits of this database to U.S. researchers. The Committee believes the results of NIH-funded research should likewise be shared with these NLM partners, further accelerating the discovery process and advancing global public health. (p. 118,119)

#### Action taken or to be taken

PubMed Central has carried out the Committee's recommendation of sharing NIH-funded research with international partners through the formation of PubMed Central International (PMCI), a collaboration among NIH's NLM, the publishers whose journal content makes up the PubMed Central (PMC) archive, and organizations in other countries that share NLM's interest in archiving life sciences literature. The long-term goal of PMCI is to create a network of digital archives that can share all of their respective locally deposited content with others in the network. The principle of international collaboration in PMCI is patterned on the demonstrated success of international data sharing of DNA sequence information, represented by NIH's Genbank database and databases in the UK and Japan. That collaboration has played a significant part in the rapid advances made in genetic studies over the past 30 years. NLM currently supports two PMCI centers: UKPMC and PMC Canada.

**UKPMC** is sponsored by the Wellcome Trust and several other major research funders in the UK, including the Medical Research Council and the National Institute for Health Research, and became operational in January 2007. In addition to the published articles it receives from the U.S. PMC archive, it also receives NIH-funded author manuscripts from the U.S.- and Canadian-funded author manuscripts from PMC Canada. In turn, it also accepts and processes author manuscripts of journal articles funded by various agencies in the United Kingdom and makes them available to U.S. PMC and PMC Canada.

**PMC Canada** became operational in October 2009, under an arrangement with NLM similar to that for UKPMC. PMC Canada represents a partnership between the Canadian Institutes of Health Research (CIHR), the National Research Council's Canada Institute for Scientific and Technical Information (NRC-CISTI), and the NLM. Like the UKPMC, PMC Canada receives final published content through the US PubMed Central. Since April 2010, PMC Canada accepts CIHR-funded author manuscripts which are made available to the U.S. and UK sites. In turn it receives NIH-funded and UK-funded manuscripts.

NIH is committed to maintaining its partnerships with both UKPMC and PMC Canada in the interest of advancing research and addressing global health issues.

## Office of the Director (OD)

### Senate Significant Items

#### Item

***Amyotrophic Lateral Sclerosis (ALS)***-The Committee urges the NIH to collaborate and develop partnerships with voluntary health associations and Government agencies, including the Food and Drug Administration, in implementing programs targeting those with ALS and other conditions with unmet medical needs. NIH's collaboration with FDA to fast track innovations that focus on translational and regulatory science is an example of the type of partnership that may speed the delivery of new treatments to people with ALS. (p. 121)

#### Action taken or to be taken

The NIH supports a number of efforts to accelerate therapy development for amyotrophic lateral sclerosis (ALS). Several new translational studies were funded by the American Recovery and Reinvestment Act (ARRA), two of which are developing new animal models to understand how newly discovered ALS gene mutations underlie ALS pathology. Other NIH ALS studies funded by ARRA include an effort to develop a platform for full genome sequencing to identify rare genetic variants underlying ALS, a multi-center ALS biomarker validation study, and efforts to generate and characterize ALS induced pluripotent stem cells. Non-ARRA funded translational research studies include a novel cell-based high throughput screening assay to identify neuroprotective agents for ALS, and pre-clinical evaluation of a novel small molecule that may lead to clinical studies of a potential ALS therapy.

The NIH actively collaborates with the Food and Drug Administration (FDA) to accelerate drug discovery and therapy development. This year, the NIH-FDA Leadership Council was established so the two agencies can work together to help ensure that regulatory considerations are a fundamental element of biomedical research planning. The trans-agency partnership is supporting a regulatory science research initiative, led by NINDS and administered with NIH funds, to encourage studies on novel approaches to improve development and regulation of new medical products. The NINDS, the lead NIH IC for ALS research, also regularly engages the scientific and regulatory expertise of the FDA's Center for Biologics Evaluation and Research (CBER). Through a Memorandum of Understanding agreement, FDA CBER experts provide advice to guide planning of NINDS sponsored preclinical studies, including recently for ALS projects. Partnering with the FDA to ensure NIH investigators are conducting their preclinical research in accordance with FDA regulatory standards will help accelerate development and delivery of new therapies for ALS patients.

The NINDS is developing Common Data Elements (CDE) for multiple disease areas to standardize research data collection in order to reduce clinical study start up times, enhance collaborations, and accelerate data analysis. Development of ALS CDEs is

underway and the NINDS has engaged the Muscular Dystrophy Association (MDA) and the ALS Association (ALSA) in this effort.

The NINDS regularly partners with other organizations to host workshops. The NINDS and the FDA co-sponsored and co-organized a workshop in September of 2010 called “Antisense Oligonucleotide (AON) Therapies in Neuromuscular Disease”. At this workshop, the two agencies together with the research and advocacy communities discussed scientific advances and regulatory issues related to AON therapies in four different neuromuscular diseases including ALS. In addition, the NINDS is partnering with the ALSA to sponsor and organize a workshop to discuss strategies for developing ALS and frontotemporal dementia disease models and the lessons learned from analysis of current model systems. The workshop, called “Advances in Disease Modeling for ALS and FTD”, will be held in conjunction with the 2010 Society for Neuroscience Annual meeting and will involve participants from the MDA, the Robert Packard Center for ALS Research, and Prize4Life, a nonprofit organization dedicated to accelerating the discovery of treatments and cures for ALS.

#### Item

***Autoimmune Diseases*** – the Committee urges the Director to facilitate increased basic research on environmental triggers and biomarkers of autoimmune diseases in collaboration with the Directors of related research Institutes through the NIH Autoimmune Diseases Coordinating Committee. The Committee believes that basic research is needed to identify the mechanisms that drive the autoimmune response. (p. 121)

#### Action taken or to be taken

NIAID is committed to advancing the understanding of the causes of autoimmune diseases, and to promoting the application of basic research to clinical investigations in order to develop more effective therapeutic approaches and prevention strategies. In support of this mission, NIAID chairs the NIH Autoimmune Diseases Coordinating Committee (ADCC), established by Congress in 1998 to increase collaboration and facilitate coordination of autoimmune disease research among NIH Institutes and Centers (ICs), other Federal agencies, and private health and patient advocacy groups.

The NIAID Autoimmunity Centers for Excellence (ACE), co-sponsored by the National Institute of Dental and Craniofacial Research (NIDCR), and the NIH Office of Research on Women’s Health (ORWH), conduct collaborative research on autoimmune diseases, including clinical trials of immunomodulatory therapies and mechanistic studies of the underlying disease process and action of the therapy, and support partnerships among clinicians and basic researchers to facilitate the identification of effective immune tolerance induction and immune modulation strategies to prevent or treat disease and accelerate the translation of scientific advances to the clinic. NIAID is also supporting innovative research conducted through its Immune Tolerance Network (ITN) to evaluate novel, tolerance-inducing therapies for autoimmune diseases, conduct integrated mechanistic studies, and develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in autoimmune diseases.

NIAID and other NIH ICs support research on environmental triggers and the development of autoimmune diseases. For example, as part of the NIH Human Microbiome Project, NIAID supports studies of the role of the human microbiome in the onset, progression, and treatment of autoimmune diseases. NIDDK supports the Environmental Determinants of Diabetes in the Young study, in which over 8,000 high-risk infants are being followed from birth through 15 years of age. Scientists regularly collect biosamples from the children, generating an enormous resource for basic research toward the identification of environmental factors and new biomarkers of type 1 diabetes. Under the FY 2010 initiative, NIH Epigenomics of Human Health and Disease, NIEHS and 12 other ICs will fund highly innovative research on the epigenetic basis of human disease, including autoimmune diseases, to elucidate the interactions among genes and environmental influences.

NIH also is working aggressively to improve understanding of autoimmunity. For example, the National Cancer Institute (NCI) is supporting research on the mechanistic basis of autoimmunity and exploring the interface between anti-tumor activity and immune responses. NCI intramural investigators studying T cell-mediated immunity have identified a novel activation pathway that may give researchers new therapeutic targets for autoimmune diseases. Other NCI intramural researchers are studying T cells in order to generate more effective anti-tumor responses without the adverse effects of autoimmunity and to better understand certain autoimmunity correlates that may be associated with multiple sclerosis and other autoimmune disorders. NIDDK is encouraging basic research on autoimmunity and the identification of new biomarkers of type 1 diabetes through a new research solicitation. NIAMS also supports research investigating the fundamental aspects of autoimmunity. For example, one study examined the relationship between established risk genes, environmental factors, and the specific autoimmune response to an autoantibody in three, well-characterized rheumatoid arthritis patient cohorts. NIAID will continue to foster trans-NIH collaborations and research activities on autoimmune diseases through the NIH ADCC.

#### Item

**Basic Behavioral and Social Sciences** – The Committee is pleased that the Basic Behavioral Opportunity Network (OppNet) was launched in fiscal year 2010 with the support of 24 Institutes and Centers and the NIH Director. The Committee has addressed basic behavioral science in many previous reports, and it applauds NIH's recognition that basic behavioral research is essential in efforts to improve the Nation's health. The Committee understands that OppNet represents a minimum of a 5-year, cross-NIH initiative designed to fill critical gaps in the NIH's basic behavioral research enterprise. The Committee requests an update on OppNet's progress in the fiscal year 2012 Congressional budget justification. (p. 120)

#### Action taken or to be taken

The NIH is pleased to report that OppNet has made significant progress since its launch in the fall of 2009. The Directors of the National Institute on Aging and National Institute of General Medical Sciences provide scientific leadership as Steering Committee co-chairmen; the Office of Behavioral and Social Sciences Research provides a full-time

OppNet Facilitator to manage and support the initiative. In FY 2010 OppNet solicited applications and awarded 35 competitive revisions for \$7.1 million to add basic science projects to existing research project grants. OppNet also awarded eight competitive revisions to Small Business Innovation Research/Small Business Technology Transfer projects for \$1.6 million, and 16 career grants to mid-career and senior scientists for training opportunities in basic social/behavioral sciences or for basic researchers who seek training in complementary areas for \$1.6 million.

OppNet also initiated a strategic planning process during FY 2010 that included the issuance of a Request for Information on health and well-being issues and what opportunities they present for future basic behavioral and social research for NIH. Members of the NIH, the extramural community, and the general public responded through an online process. Their 352 collective responses informed a planning process that resulted in the issuance of 10 funding opportunity announcements for fiscal year 2011 in basic biobehavioral mechanisms related to sleep and social environments, basic mechanisms of behavioral maintenance, building intellectual capacity in basic behavioral/social sciences, self-regulation mechanisms, and psychosocial stress-related issues-including the development of comprehensive and conceptually-based measures, and the integration of behavioral and psychosocial processes. To continue public involvement in its strategic planning process, OppNet held an open conference October 28-29, 2010 to solicit information on health-related research directions in the basic behavioral and social sciences and OppNet's potential response to these exigencies in the short- and longer-terms before the scheduled sunset date of September 30, 2014.

#### Item

**Basic Cell Research** – The Committee believes that the funding of basic biomedical research is an important investment in the future health and well-being of our Nation. Ideas that may one day result in the development of cures and treatments for cancer and other diseases begin with basic research into the understanding of how cells work. The Committee believes that basic biomedical research should remain a key component of both the intramural and extramural research portfolio at the NIH. (p. 121)

#### Action taken or to be taken

The NIH agrees with the Committee's assessment that the funding of basic biomedical research represents a critical, long-term investment needed to ensure the future health and well-being of our Nation. The NIH's commitment to basic biomedical research is reflected in the research portfolios of its Institutes and Centers, as well as the NIH Common Fund. Most of the reporting categories used to report NIH investments include basic cell research. For example, a substantial component of the Polycystic Kidney Disease (PKD) funding is basic cell research to understand the formation and function of the primary cilium that decorates kidney epithelial cells. Through basic cell research, investigators have discovered that malformation of this cellular structure is the basis for PKD as well as other cystic kidney diseases. This has, in turn, led to the realization that syndromic features associated with certain kidney diseases are also due to dysfunction of the primary cilia in other tissues. This scenario has played out countless times in research. Basic cell biology is a fundamentally important part of the biomedical research

continuum because it underlies virtually every disease or condition. NIH is committed to basic research and it will remain a significant investment across the NIH.

#### Item

**Career Development Awards** - the Committee recognizes the role of clinical researchers as a primary resource for advancement and innovation in biomedical science. In order to ensure and expand the pool of highly talented patient-oriented researchers, the Committee supports the preservation of K awards as a critical training mechanism. (p. 121)

#### Action taken or to be taken

NIH shares the Committee's view of clinical researchers as vital contributors to the advancement of biomedical research, and is committed to maintaining the career development activities (i.e., K awards) that allow clinicians to bolster their research skills and become independent investigators.

With the introduction of the Mentored Patient-Oriented Research Career Development Award (K23) and Midcareer Investigator Award in Patient-Oriented Research (K24) in 1999, and the institutional career development awards associated with the Clinical and Translational Science Awards program (CTSA) in 2006, much of NIH's career development support for patient-oriented clinical investigators is now concentrated in these three activities. In FY 2009, NIH made a total of 1,018 K23 awards, 276 K24 awards, and provided career development support to more than 300 individuals at 46 CTSA sites.

In their efforts to reduce the time it takes for laboratory discoveries to become treatments for patients, CTSA sites around the country provide a particularly rich environment for promoting multidisciplinary approaches to clinical studies and are an excellent setting for developing the careers of patient-oriented researchers. Because the development of clinical researchers is such an important part of NIH's mission, an evaluation of the CTSA program and its career development activities is currently underway. The career development component of the evaluation is focused on the collection and analysis of data based on surveys of scholars, trainees and mentors at the CTSA institutions as well as the analysis of data in Annual Progress Reports submitted by CTSA institutions. The surveys will provide insight into trainee/scholar career pathways, research accomplishments, and satisfaction with mentoring and advanced degree granting clinical and translational science programs.

Another recently completed evaluation of NIH's individual mentored career development award found that K23 awardees obtain NIH research grant support and publish research findings at significantly higher rates than individuals with similar research backgrounds who did not receive these awards<sup>17</sup>. The success of these career awardees provides compelling reasons for NIH to continue supporting these programs.

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<sup>17</sup> Schnell, J. *An Evaluation of the NIH Program of Individual Mentored Career Development Awards*. Presented to the NIH Training Advisory Committee, September 8, 2010.

#### Item

***Class B Animal Dealers***- the Committee noted with strong interest the April 2010 report issued by the NIH titled "The Use of Random Source Class B Dealers in NIH-Supported Research." The report concludes that the best way to phase out the use of class B dealers as the providers for random-source dogs and cats in NIH-supported research is to supplement class A dealers so that they can provide these animals instead. The 3- to 4-year timeline projected by the NIH to complete this transition is longer than the Committee would have preferred, especially considering that the NIH largely ignored this issue for years. However, the Committee is pleased that the NIH is on track to meet the early milestones of this timeline. The Committee expects this pace to continue and requests an update in the fiscal year 2012 congressional budget justification. (p.122)

#### Action taken or to be taken

The NIH has developed and is implementing an aggressive acquisition plan that will support development of Class A vendor source/s to breed mature, large, socialized, out-bred hounds or mongrel research dogs to replace dogs now acquired through Class B dealers. The acquisition plan is due to begin in FY 2011 with a small number of animals available initially. These numbers will increase each year with a majority of animals available in FY 2014 and full phase-in anticipated by 2015. Due to the need to establish new breeding colonies, and the time necessary to breed, whelp, wean, socialize, and raise animals to a size and age necessary for research purposes (approximately 2 years), the phase-in must be done over a period of several years. NIH is working on a policy statement for the research community informing them of the transition and eventual phase out of research animals provided by Class B vendors and encouraging researchers to begin planning for this transition as soon as possible. NIH expects to issue this policy statement in the NIH GUIDE in early 2011, after the award of the acquisition plan.

#### Item

***Clinical and Translational Science Awards (CTSAs)*** - The Committee strongly supports the CTSA program, a nationwide network of research institutions that aims to increase the translation of basic science, speed the delivery of treatments and cures to the public, and foster the development of the next generation of diverse, highly trained clinical and translational science professionals. The Committee believes that greater involvement from all 27 Institutes and Centers [ICs] would help the program reach its full potential. Therefore, the Committee requests that the Director consider developing a formal, NIH-wide plan on how to align the CTSAs with the programmatic and funding priorities of the ICs. (p.122)

#### Action taken or to be taken

The NIH created the Clinical and Translational Science Awards (CTSAs) program in 2006 to catalyze the development of a new discipline of clinical and translational science to facilitate research across the NIH Institutes and Centers (ICs) and the

broader research community. The program, funded jointly by the NIH Common Fund and the National Center for Research Resources (NCRR), provides assistance to academic institutions to establish an integrated academic home to train and nurture multi- and inter-disciplinary investigators and research teams, establish an incubator for the development of innovative research tools and information technologies, and synergize multi-disciplinary clinical and translational research. The CTSA program has produced a consortium of 55 research centers. A multi-IC CTSA Advisory Board has been convened to help ensure the success of the CTSA's and continued engagement of the trans-NIH community. The Board consists of seven NIH Institute Directors and the DPCPSI Director and meets three to four times annually to provide input and guidance to the NCRR Director on the implementation and direction of the CTSA's program. However, the Board is advisory only and does not have had direct oversight authority. The structure and oversight of the CTSA's are currently being reconsidered.

#### **Item**

**Communication of Research Findings** - The Committee is pleased that the NIH has continued to support NIH MedlinePlus magazine, which provides consumers and health professionals with easy-to-read health information based on the latest NIH-supported research, and a new bilingual version of the magazine, NIH MedlinePlus Salud. While the bulk of the support for the magazine comes from the NLM, the Committee urges the Director to work with the Institutes and Centers to provide the resources necessary to increase the distribution of these important sources of consumer health information to reach all physician offices, federally qualified health centers, hospitals, libraries and free-standing health clinics. (p. 122)

#### **Action Taken or To Be Taken**

NIH research has produced cutting-edge treatment strategies while moving science forward in a variety of biomedical fields. As part of the agency's congressionally mandated public education and outreach mission, the NIH institutes and centers sponsor a robust program of information development and dissemination. The NIH pursues all possible appropriate outlets for science and health information dissemination while increasing public understanding of the benefits and health outcomes of Federally-supported research. ICs provide content and technical review of materials designed to address specific health conditions, prevention strategies, and treatments. This allows NIH to convey clear, accurate, culturally-appropriate, and scientifically-vetted health information to a range of audiences in a number of languages.

The NIH continues to explore every available outlet for better communication of research findings to health consumers throughout the United States and abroad. NIH has long supported NLM's *MedlinePlus* website and magazine, both of which offer information that originates from NIH component ICs. Like the vast majority of NIH information products, *MedlinePlus* is available both electronically and in hard copy format, allowing for broad ease-of-access for health consumers and providers. NIH distributes agency-produced information at health events, professional scientific meetings, and through the agency's information clearinghouses and contacts. With rare

exceptions, single copies of NIH information products are available to the public upon request at no cost and are also free from commercial advertising.

In recent years, NIH has redoubled efforts to maximize partnerships with private sector entities, including nonprofits, academic health institutions, and healthcare networks. The NIH continues to explore opportunities for joint collaborations, acknowledging the private sector's critical role in NIH-supported research and health information dissemination. Individuals, organizations, and institutions are encouraged to request copies, including bulk copies, of all NIH publications, and to work with NIH ICs on expanding opportunities for collaborative programs that meet mutual health communications goals and objectives.

The NIH pledges to remain committed to maximizing agency resources devoted to production and dissemination of NIH information, including *MedlinePlus*, recognizing the magazine's role as part of the agency's portfolio of reliable and authoritative health information.

#### Item

**Diabetes** - The Committee recognizes that more research and education is needed on the disparate effects of diabetes on minority populations. Therefore, the Committee urges the NIH to expand, intensify, and support ongoing research and other activities with respect to pre-diabetes and diabetes in minority populations, including research to identify clinical, socioeconomic, geographical, cultural, and organizational factors that contribute to diabetes in such populations. Specifically, the Committee encourages NIH to research behavior and obesity; environmental factors that may contribute to the increase in type 2 diabetes in minorities; environmental triggers and genetic interactions that lead to the development of type 2 diabetes in minority newborns; genes that may predispose individuals to the onset of type 1 and type 2 diabetes and its complications; methods and alternative therapies to control blood glucose; and diabetic and gestational diabetic pregnancies in minority mothers. The Committee also asks that the NIH, through the NIMHD and the National Diabetes Education Program, mentor health professionals to be more involved in weight counseling, obesity research and nutrition; provide for the participation of minority health professionals in diabetes-focused research programs; and encourage increased minority representation in diabetes-focused health fields. (p. 122,123)

#### Action taken or to be taken

The NIH is committed to combating the epidemic of type 2 diabetes in the U.S., and to reducing or eliminating the disparity which disproportionately burdens minority populations with the disease. Accordingly, major NIDDK type 2 diabetes clinical studies include a large proportion of participants from these groups of Americans. Such studies include the previously reported Diabetes Prevention Program (DPP) and Look AHEAD clinical trials, as well as the HEALTHY trial, which tested a school-based intervention for reducing diabetes risk in middle schools with a high proportion of minority students at risk for the disease; and TODAY, which is testing three different treatment strategies in young people with type 2 diabetes. The NIDDK is also studying the biological

underpinnings of this important health disparity through the Type 2 Diabetes Genes Consortium, which aims specifically to define genes contributing to this disparity. NIMHD Centers of Excellence investigate clinical, socioeconomic, geographical, cultural, and organizational factors that contribute to diabetes in minority populations. Projects include research exploring genetic risk factors for metabolic syndrome in minority populations, diabetes self-management models, possible associations between vitamin deficiency and diabetes, early markers of pre-eclampsia in diabetic minorities, and the use of traditional healing practices in preventing diabetes and its complications. NIMHD also supports research on diabetes and obesity during pregnancy.

Ongoing NIDDK-supported translational research efforts focus on ensuring that scientifically proven strategies for controlling or preventing diabetes become accessible to those who need them most. In recent trials, group-based intensive lifestyle interventions modeled after the DPP and delivered by trained community workers and/or staff at YMCAs demonstrated sustained weight loss similar to that achieved and shown to be highly effective in the DPP, but at significantly lower cost. This model, coverage for which is already being tested by at least one health insurance group, has the potential to deliver a low cost intervention with efficacy similar to that of the DPP. NIMHD is supporting diabetes prevention efforts in Native Hawaiian and Pacific Islanders utilizing a lifestyle intervention similar to that used in the DPP, and diabetes management efforts in Mexican-American populations.

The NIDDK-CDC National Diabetes Education Program (NDEP) translates the latest science and spreads the word that diabetes is serious, common, and costly, yet controllable and, for type-2 diabetes, preventable. NDEP features a host of culturally tailored publications for patients translated into a variety of languages, and a series of important and proven, successful tools for healthcare professionals. Other educational efforts include the Diabetes Education in Tribal Schools program, and the Diabetes Education Curriculum for K-12 Schools initiative, which seeks to reduce the incidence and prevalence of type 2 diabetes among African American and Hispanic youth and to increase interest in biomedical careers by developing, implementing, monitoring, and evaluating effective and sustainable science-based diabetes education supplemental curricula for K-12 schools that have predominantly African American and Hispanic/Latino students. NIMHD Loan Repayment Program (LRP) is aimed at recruiting and retaining qualified health professionals to research careers that focus on minority health or health disparities issues. Some scholars participating in the LRP are also engaged in diabetes-related research. The NIMHD Disparities Research and Education Advancing our Mission (DREAM) Career Transition program supports the transition of graduates of the LRP program, to independent investigators. DREAM participants spend two years in the NIH Intramural Research Program and are placed with other NIH ICs based on their research interests where they are mentored by a senior investigator.

#### Item

**Down Syndrome** - The Committee is pleased that the NINDS is co-hosting a conference in December to further identify and explore the issues involved in the development of a national Down syndrome patient registry and one or more biobanks, and it encourages additional support for this effort. As increased Federal funding for translational research is important to fostering a better understanding of Down syndrome and exploring therapeutic treatments, the Director is encouraged to dedicate sufficient resources to the implementation of the 2007 NIH Research Plan for Down syndrome. Finally, the Committee continues to urge the NIH to establish workshops and mentoring programs to encourage young researchers and scientists to successfully pursue NIH grants for Down syndrome research. (p.123)

#### Action taken or to be taken

In 2007, NICHD successfully led the trans-NIH Working Group on Down Syndrome in an effort to develop the NIH Research Plan for Down syndrome. Since the release of the Research Plan, the number of grant applications relevant to Down syndrome escalated significantly. Prior to the release of the Research Plan, about 40 Down syndrome-related applications were considered by the various NIH Institutes and Centers, and 11 were funded. NICHD and NIA issued a Request for Applications entitled "Factors that Affect Cognitive Function in Adults with Down Syndrome," and two applications received funding. These investigators are using longitudinal natural history studies and various functional and structural brain imaging techniques to determine biomarkers that may identify those adults with Down syndrome who are at risk for developing Alzheimer-like dementia. Also, in FY 2009, 11 grantees received either two-year funding from the American Recovery and Reinvestment Act (ARRA) or ARRA administrative supplements from NICHD, including five new or early-stage investigators.

In FY 2010, 340 applications were received by NIH with many in response to Grand Opportunity and Challenge grants. Of those, 51 were funded, 14 by NICHD. In addition, ARRA funds made available in FY 2010 provided support for one new award and three supplements to existing awards. Since the release of the Research Plan, NICHD also has supported several important scientific meetings, including one focused on mosaic Down syndrome.

NICHD is committed to providing the necessary research resources to allow scientists to proceed with their work as quickly as possible. In September 2010, a long-standing contract to ensure availability of suitable mouse models for studies relevant to Down syndrome was renewed through 2015 at substantially higher levels of funding. In addition, NICHD participated in a conference sponsored by the National Down Syndrome Society in September 2010 that included researchers, parent and research advocacy organizations, and Federal agencies to begin planning a Down syndrome registry. Building on that meeting, NICHD partnered with the Global Down Syndrome Foundation to hold a conference in December 2010 on the spectrum of resources needed to move this field of research forward, including a registry, database, and biobank.

Item

***Dystonia Consortium*** - The Committee commends the ORDR for providing funding for 19 research consortia including the Dystonia Coalition, as part of the second phase of the Rare Diseases Clinical Research Network. The Committee requests an update on the Dystonia Coalition research activities in the fiscal year 2012 congressional budget justification. (p. 120)

Action taken or to be taken

As requested by the Committee, the Office of Rare Diseases Research (ORDR) is providing an update on the Dystonia Coalition. The Dystonia Coalition is a collaboration of medical researchers and patient advocacy groups supported by the ORDR and the National Institute of Neurological Disorders and Stroke at the NIH. The Dystonia Coalition is one of the 19 consortia of the Rare Diseases Clinical Research Network. The consortium's goal is to advance the pace of clinical and translational research in the dystonias to find better treatments and a cure. Specific objectives are to develop a fuller understanding of the many different features of dystonia and how they change over the years, to develop validated diagnostic strategies and rating tools for diagnosis and monitoring patients in clinical trials, to establish a biorepository where samples of blood and other materials can be stored and distributed for research, to catalyze clinical trials for promising new treatments, and to promote education and awareness.

In its first year, as the necessary approvals for the first clinical studies are progressing, the consortium has made progress in developing an effective collaborative organization and enrolling potential participants in several planned clinical studies that will begin in the near future. The consortium has grown from the original 18 sites to a collaborative community that includes 40 participating clinical sites in 9 countries, working with 9 patient advocacy groups as well as private-sector pharmaceutical companies. The broad distribution of sites will greatly facilitate enrolling participants thereby greatly facilitating research projects. In addition to enhancing the collaborative spirit among stakeholders, the consortium has fostered the enrollment of junior and senior investigators in clinical training programs in the dystonias.

Currently, three projects are nearing approval: A Natural History and Biospecimen Repository for Focal Dystonia; A Comprehensive Rating Tool for Cervical Dystonia; and establishing Validity and Reliability of Diagnostic Methods and Measures of Spasmodic Dysphonia. In addition, the pilot project program is proceeding with five studies. One study is nearing completion and the other four are awaiting approvals. Two pilot projects address primary dystonia and one project each: Primary blepharospasm, idiopathic cervical dystonia, and focal dystonia. The training program is funding two junior and one senior investigator.

The participating patient advocacy groups have partially supported the pilot project program, the training program, primary projects, and an annual meeting. They have also collaborated in determining which contact registry in the dystonia community might be most efficacious to utilize.

#### Item

**Fibromyalgia-** The Committee recognizes that fibromyalgia is a disorder that impacts the lives of millions of Americans and is deeply concerned regarding the lack of a sustained commitment to fibromyalgia-specific research at the NIH. While NIAMS has been the lead Institute for fibromyalgia, the NINDS should also play a key role because of substantial evidence implicating pathology within the central nervous system in the development and expression of fibromyalgia symptoms, including abnormal brain activity, abnormal concentrations of a variety of neurotransmitters in cerebrospinal fluid, dysautonomia and neuroendocrine dysfunction. The Committee urges both Institutes to stimulate interest in this field by supporting additional research through all available funding mechanisms and by convening a conference to open the door to new scientific findings. Areas of particular interest include neurotransmitter abnormalities and other neurological problems revealed by prior brain and cervical neck imaging studies, as well as further investigation of sleep disturbances and genetic factors. (p.123)

#### Action taken or to be taken

Fibromyalgia syndrome is a common and chronic disorder characterized by widespread pain, diffuse tenderness, cognitive and memory problems, and a number of other symptoms. Approximately 5 million Americans over age 18 are affected by the syndrome, for which no specific cause has yet been identified.

In 2010, as part of a series of roundtable meetings organized by NIAMS, researchers came together to discuss the impact of psychosocial and behavioral therapies on musculoskeletal and rheumatic disease outcomes, including those associated with fibromyalgia. Through these annual roundtables, the NIAMS leadership and scientific staff had an opportunity to discuss the most pressing issues under consideration by both researchers and patients. This helps position the Institute to appropriately guide our research efforts and, ultimately, improve the health of the American public.

Through a collaborative effort by NIAMS, NINDS, NIDCR, and NCCAM, along with the American College of Rheumatology, a scientific meeting, "Pain and Musculoskeletal Disorders: Translating Scientific Advances into Practice," was held on the NIH campus in December 2010. The meeting was organized by leaders from the rheumatology community and brought together internationally recognized experts in a broad range of disciplines, spanning musculoskeletal and rheumatic diseases to pain and other sensory symptoms, in an effort to stimulate interdisciplinary collaborations. Presentations included advances in pain research covering basic science, genetics, novel treatments, and variation across special populations, including women and minorities. The knowledge shared will have an important impact on research in fibromyalgia and other conditions of chronic pain.

NINDS continues to support a large portfolio on understanding and treating pain including the chronic, unexplained pain found in fibromyalgia. NINDS-funded projects include grants to identify the circuits in the peripheral and central nervous systems and the modulators of these circuits that contribute to pain. NINDS-funded researchers are

studying hormonal controls of pain and contributions of the neurotransmitters glutamate and GABA to persistent pain. A number of recently funded grants focus on the role of calcium and other ion channels; these channels are targets for a number of drugs that are used to treat pain associated with fibromyalgia and other conditions. Studying the structure of these channels will help to better understand how drugs interact with the channels and aid in refining treatments for these disorders. NINDS-funded researchers are also looking for ways to target potential pain-treatment drugs to the central nervous system, including a grant to develop ways for small proteins (peptides) to penetrate the blood-brain barrier.

#### Item

**Health Disparities Research in Women:** Women of racial and ethnic minority populations face higher rates of diseases including obesity, cancer, diabetes, heart disease, and HIV/AIDS, when compared with white women. There is also a disproportionately higher rate of pre-term birth among African-American women that cannot be accounted for by known risk factors. The Committee encourages the ORWH to support research into the causes of health disparities and develop and evaluate interventions to address these causes. The Committee also understands that continued and expanded collection of data capturing racial and ethnic information is essential in understanding and reducing disparities. (p.120)

#### Action taken or to be taken:

To address the higher rates of diseases and conditions faced by racial and ethnic minority populations, including women, the National Institute on Minority Health and Health Disparities (NIMHD) coordinates NIH's health disparities research efforts among the Institutes and Centers (ICs) including the Office of Research on Women's Health (ORWH), through the NIH Health Disparities Strategic Plan and Budget. The ORWH specifically coordinates NIH's research efforts focused on women, including women of racial and ethnic minority populations. In addition, ORWH collaborates with the NIH ICs to ensure the inclusion of women of racial and ethnic minority groups in NIH-supported clinical research. As addressed in the NIH Strategic Plan for Women's Health Research, ORWH promotes and co-funds research on several diseases and conditions, including obesity, cancer, diabetes, heart disease, and HIV/AIDS. Following are examples of research supported by the ORWH and the NIMHD to address the high rates of diseases in women of racial and ethnic minority groups.

ORWH co-funds the National Institute of Diabetes and Digestive and Kidney Diseases Diabetes Prevention Program (DPP), a landmark study now in its 17<sup>th</sup> year of funding, which is the largest and most diverse study (86% are minority) of individuals with pre-diabetes. The DPP confirmed that lifestyle changes and drug interventions can markedly reduce the risk of developing type-2 diabetes. The ORWH also co-funds the *Eunice Kennedy Shriver* National Institute on Child Health and Development study recruiting a racially/ethnically/geographically-diverse population of 10,000 first-time mothers to study the mechanisms for, and prediction of, adverse pregnancy outcomes such as preterm birth, preeclampsia, and fetal-growth restriction. Disseminating information about health disparities to the public and health professionals is an

important and widely used strategy by NIH ICs. The ORWH has published multiple editions of the *Women of Color Health Data Book* and has created a new series, the *Women of Color Health Information Collection*. NIMHD research programs are making progress in understanding the complex interactions of the social, biological, and behavioral factors contributing to the persistence of health disparities. Researchers are advancing in unraveling the contributions of access to care, quality of care, and interventions, such as treatment of periodontal disease in pregnancy, to birth outcomes. Researchers investigating disparities in cardiovascular disease found lower serum levels of 25-hydroxyvitamin D in women, elderly persons and participants with obesity, hypertension and diabetes mellitus. Researchers investigating breast cancer disparities have determined that a gene that regulates fetal development and survival of breast cancer cells may contribute to lower breast cancer survival rates experienced by African American women.

NIMHD recognizes the need to expand and enhance current data collection efforts to include primary language, racial and ethnic subpopulations, and populations residing in rural and medically underserved areas. These efforts and others are part of NIMHD's Health Disparities Strategic Plan and these goals are fully consistent with Congressional language set forth in the *Patient Protection and Affordable Care Act*, P.L.111-148. In 2009, NIMHD established a data collection coordinating center to assist NIMHD in capturing such data. ORWH, NIMHD and the other ICs will continue promoting and funding research which addresses health disparities experienced by racial and ethnic minority women.

#### Item

**HIV/AIDS Behavioral Research-** The Committee urges the NIH to support behavioral research aimed at reducing the likelihood of HIV infection by determining risk factors in various populations as well as the ways in which interventions need to be tailored for specific populations at greatest risk of becoming infected. (p. 128)

#### Action taken or to be taken

The NIH Office of AIDS Research (OAR) will continue to ensure the availability of funds to the NIH Institutes and Centers to support research on risk factors and interventions for specific populations and settings. NIH also will encourage the integration of biomedical and behavioral perspectives to create interdisciplinary approaches and knowledge. The Behavioral and Social Science Planning Group convened by OAR to develop the annual Trans-NIH Plan for AIDS-Related Research recommended focus on several priority areas, including (1) development of further understanding of biological-behavioral interactions and social-environmental influences on HIV transmission risks; (2) continued study of disparities in HIV infection rates among racial and ethnic communities; (3) interventions targeting communities with high needs for prevention interventions; (4) integration of state-of-the-art behavioral science into clinical trials; and (5) expansion of laboratory-based behavioral and social methods to more intensively investigate risk behaviors.

Early NIH-funded studies evaluated risk by associating specific behaviors with AIDS, and later, with HIV transmission. Over time sophisticated, comprehensive models incorporating multiple behavioral and social variables emerged to measure the risk attributable to specific behavioral and social factors and to quantify relationships among variables. For example, an NIH-funded study of HIV risk in women in the early 1990s used measures of substance use, sexual experience, victimization, beliefs about partners, assertiveness, psychosocial functioning, sexual functioning, and attitudes about AIDS prevention to explain 70 percent of the differences in individual women's HIV risk through unprotected sexual intercourse and to show how the social and behavioral factors interact. Similar quantitative approaches have been used in drug users, minority populations, adolescents, and men-who-have sex-with men (MSM).

Despite the advances made in the past two decades in understanding and predicting risk behaviors, much remains to be accomplished in translating these research findings and reducing HIV transmission rates. Overall, studies have shown that existing behavioral interventions can reduce risk behaviors by about 25 to 50 percent depending on the intervention, population, and outcomes measured, with much less success in changing HIV incidence rates. One of the best estimates of the impact of behavioral strategies comes from a Cochrane review showing that behavioral interventions result in a 17 to 27 percent reduction in HIV risk behaviors among MSM. Although it is counter-intuitive, a focus on risk behaviors alone is insufficient to have major impact on transmission. Data from the CDC have shown that differences in rates of risk behavior do not explain differences in rates of HIV infection among black MSM. That is, persons with HIV did not differ from those who did not have HIV in terms of risky behaviors. This finding is congruent with the models of risk in various populations that showed many variables are needed to explain risk. This finding also serves as a stark reminder that even the best models still leave critical pathways of HIV transmission unexplained. NIH research will continue to investigate combination strategies that integrate and address social, behavioral, and biomedical factors.

#### Item

**Lupus** - The Committee continues to support additional basic, clinical and translational research on lupus. (p.123)

#### Action taken or to be taken

Lupus is an autoimmune disease, one of several disorders of the immune system. Lupus can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Although people with the disease may have different symptoms, some of the most common ones include extreme fatigue, painful or swollen joints (arthritis), unexplained fever, skin rashes, and kidney problems.

The NIH supports basic research aimed at identifying novel targets for the use of existing drugs for patients with lupus, as well as laying the foundation for the development of new therapies to treat this disease, some of which are currently in clinical trials. Existing drugs often have a proven safety profile, making them more

readily available for patients to begin treatment once their efficacy has been established.

For example, NIAMS intramural researchers have discovered that the activation of basophils, a type of immune cell known for its role in allergy, causes kidney damage in a mouse model of lupus. These findings and the team's associated research in humans have opened up new avenues of investigation for lupus treatment, such as targeting basophils. A promising potential treatment is omalizumab, a medicine which works by blocking the actions of basophils, and is already on the market to treat allergic asthma. The NIH team is currently planning a safety study of omalizumab in people with lupus.

Other NIAMS-funded researchers are studying the role of a receptor molecule, S1P1, in regulating other immune system cells. Understanding how S1P1 overrides the immune suppressing role of T-regulatory cells is an important step in unraveling the complex responses that can contribute to autoimmune diseases like lupus. These pathways represent more potential targets for therapy.

MiRNAs are very short ribonucleic acids (RNAs) that are used by cells to regulate the expression of many genes. Recently, NIAMS-supported researchers identified a unique miRNA signature that is associated with a type of lupus that affects the kidneys (nephritis), and thus may be used as a biomarker for this disease. Such biomarkers may help in predicting onset and severity of disease, and thus inform treatment. Additionally, future steps to identify the targets of these miRNAs and determine the mechanisms by which they contribute to disease pathogenesis will shed light on lupus etiology and may lead to novel therapies to treat and possibly prevent lupus.

In September 2010, NIAMS, NIAID, NCI, and the NIH Office of Research on Women's Health hosted a two-day scientific meeting, "Systemic Lupus Erythematosus: From Mouse Models to Human Disease and Treatment." Clinicians and basic scientists from a variety of disciplines came together to discuss the clinical and molecular similarities and differences seen in human disease and animal models. Participants also discussed advances in lupus genetics, challenges and advances in the treatment of lupus, and emerging areas warranting further study.

#### Item

**Lung Disease-** The Committee encourages the Director to work with the NHLBI, NIEHS, NIAID and FIC to develop cross-Institute initiatives on the causes, identification, treatment and prevention of lung disease. (p.123)

#### Action taken or to be taken

Collaboration between NIH components on research in lung diseases, including asthma, COPD, lung cancers, pulmonary hypertension, and genetic diseases such as cystic fibrosis is active and productive. In March 2010 NHLBI, NIAID, NIEHS, and NICHD co-sponsored a workshop to establish standard definitions and data collection methods for validated outcome measures in asthma clinical research and to identify new outcome measures to improve the efficiency of future clinical trials. Other Institutes

and several other agencies within the DHHS and EPA participated and are involved in follow-up meetings. NICHD, NHLBI, NIAID, and NIEHS are planning a 2011 workshop on research for asthma prevention in children. Mechanistic connections between COPD and lung cancer will be explored in a joint NHLBI–NCI program in FY 2011.

NIA, in collaboration with NIAID and NHLBI, has issued new funding opportunity announcements to encourage grant applications for basic, translational, clinical, and epidemiological studies on the pathophysiology, epidemiology, diagnosis, and management of asthma in older adults.

NIEHS, NHLBI, NIAID and NICHD have entered into an interagency agreement with the CDC National Center for Health Statistics to design and implement a supplement to the National Ambulatory Medical Care Survey about physicians' use of National Asthma Education and Prevention Program asthma guidelines. NIEHS is working with EPA on two projects under the Clean Air Act to identify mechanisms and factors that place humans at risk of environmentally induced airway disease.

For rare lung diseases, NHLBI is developing a right-heart research program to address mortality in pulmonary arterial hypertension. NHLBI partners with NCRR to support lymphangioleiomyomatosis tissue collection and distribution.

Tobacco consumption is among the most important risk factors for chronic respiratory disease throughout the world, and cigarette smoking is increasing at alarming rates in low- and middle-income countries (LMICs). The FIC supports trans-disciplinary research projects that address the burden of tobacco consumption in LMICs. For example, its International Tobacco and Health Research and Capacity-Building Program is studying the effects of indoor air pollution and smoking by household males on respiratory deaths among children and women in India. NIH partners for this program include NCI, NIDA, and NHLBI. Other international efforts include the Global Alliance for Clean Cook Stoves, a public–private partnership that seeks to reduce exposures to smoke from indoor cooking. Anticipated contributions of NIH will total approximately \$25 million over five years. The NIH will also host and co-sponsor a state-of-the-science conference on cook stove issues in the spring of 2011, which will involve the active participation of multiple NIH components, including NHLBI, NIEHS, and FIC.

#### Item

**Lyme Disease** - The Committee is encouraged that the NIH has signaled its intent to hold a scientific conference on Lyme and other tick-borne diseases in coordination with the NIAID. The Committee believes that the conference should represent the broad spectrum of scientific views on Lyme disease as well as individuals with Lyme disease. (p. 123,124)

#### Action taken or to be taken

NIAID remains committed to supporting research on the biology and pathology of Lyme disease and other tick-borne diseases to better understand and treat these diseases.

The Institute conducts and sponsors a broad range of laboratory and clinical research that aims to advance scientific knowledge of tick-borne diseases, including Lyme disease, and translate this knowledge into improved diagnostics and therapeutics for clinical use. NIAID will continue multiple lines of investigation with increasing emphasis on exploring the biological markers of infection with the causative agent of Lyme disease, *Borrelia burgdorferi*, assessment of the clinical course and outcomes of patients with Lyme infection, and the immunological response to *B. burgdorferi* infection.

NIAID, through the NIH contract with the Institute of Medicine (IOM), requested that the IOM organize and hold a scientific conference on Lyme and other tick-borne diseases that would represent the broad spectrum of scientific views on Lyme disease and include input from individuals with Lyme disease. Recognizing the IOM's longstanding ability to address pressing public health issues, NIAID is confident that the IOM will ensure a balanced, objective and independent process that represents the broad spectrum of scientific viewpoints and provides a forum for public participation and input from patients suffering from Lyme disease and other tick-borne diseases. Indeed, the NIH and DHHS agencies have frequently called upon the IOM to organize such meetings and workshops in recognition of its ability to facilitate discussions and critical thinking around a wide variety of scientific issues.

The IOM, with support from NIAID, hosted a two-day conference on Lyme and tick-borne diseases on October 11-12, 2010, in Washington, D.C. In preparation for the conference, the IOM held an open meeting in Washington, D.C., in April 2010 and held four independent telephone listening sessions to secure input from the community on Lyme disease and other tick-borne diseases. The IOM worked diligently to develop a comprehensive, two-day conference agenda that brought together a broad array of speakers to address the key scientific issues. Multiple opportunities for open discussion and public participation were included in the conference agenda.

Additionally, the IOM established a Web site to receive information from the public. As a further means of obtaining input, the IOM continues to stand ready to accept any written submissions from the general public and advocacy community. NIAID is confident that the conference will result in a report that summarizes the state of the science on Lyme and tick-borne diseases and represent the broad range of views on these diseases.

#### Item

***Lymphatic Research and Lymphatic Disease*** - The Committee applauds the Trans-NIH Coordinating Committee for Lymphatic Research for the success of recent NIH lymphatic-related symposia and for eliciting multidisciplinary extramural recommendations from a Lymphatic Research Working Group. The Committee is disappointed, however, that the NIH's June 2009 report on lymphatic research did not fulfill the Committee's request "to set forth short and long-term strategic plans to advance research of the lymphatic system and lymphatic diseases, and specifically addressing the Trans-NIH Working Group 2008 Recommendations." Therefore, the Committee again asks each of the Institutes and Centers [ICs] with an interest in

lymphatic research (NHLBI, NCI, NIDDK, NICHD, NINR, NEI, NIAID, NIAMS, NIBIB, and ORD) to set forth explicit, prospective, actionable plans and implementation strategies for each Working Group recommendation for the years 2011-2014, including but not limited to: (a) the creation of centralized core facilities for experimental molecular and diagnostic lymphatic imaging; (b) the development and standardization of research reagents; (c) the generation of virtual networks to facilitate basic, translational, and clinical research; (d) the development of techniques for the quantitative and molecular imaging of lymphatic function, lymphatic malformations, and lymph nodes; (e) the creation of interdisciplinary programs to train new investigators in lymphatic research; (f) the support of patient registries and the creation of a lymphatic disease tissue bank; (g) the generation and characterization of animal models to foster and facilitate investigations in lymphatic biology; and (h) the identification of suitable panels of biomarkers for lymphatic disease. In addition, the Committee once again urges all relevant ICs to continue to expressly include lymphatic system research in related funding mechanism requests where a lymphatic research component is appropriate. (p. 124)

#### Action taken or to be taken

An important function of the trans-NIH Coordinating Committee for Lymphatic Research (CCLR) is to facilitate interactions among researchers studying lymphatic biology in health and disease and to raise awareness of this important topic and its research needs within the intramural and extramural research communities. CCLR membership includes the following ICs: NHLBI, NCI, NIDDK, NICHD, NINR, NEI, NIAID, NIAMS, NIBIB, and ORD. Some recent activities of the CLR include a March 2009 workshop to increase collaborations within the NIH lymphatic research community; a symposium, "Lymphatic Biology and Disease: the Cinderella of the Vascular System Finally Gets Invited to the Ball," held during the NIH Research Festival in October 2009 to raise awareness within NIH; a 2-day scientific workshop, "Lymphatics in the Digestive System: Physiology, Health, and Disease," hosted by the NIDDK to highlight the future research needs on the lymphatic system in areas of NIDDK interest; and the 2010 Gordon Research Conference on Molecular Mechanisms in Lymphatic Function and Disease, supported by the NHLBI.

For fiscal years 2011-2014 short and long term strategies include plans for the CCLR to sponsor symposia on lymphatic research at national scientific conferences to continue to raise awareness of research needs in the area of lymphatic research and lymphatic disease. In addition, the NHLBI plans to include lymphatic disease in appropriate basic and translational research initiatives. The CCLR will encourage other member ICs to do the same.

The NIH plans to implement the 2008 Trans-NIH working group recommendations as follows: **a.** The NHLBI, NCI and NIBIB are supporting the development of methods for molecular and functional imaging of the lymphatic system in living organisms (animals and humans). The CCLR will facilitate the interactions between investigators involved in this endeavor that can serve as core facilities for experimental molecular and diagnostic lymphatic imaging; **b.** NIH supported research on the lymphatic system resulted in

generation of several reagents that are shared by the investigators in this field; **c.** The CCLR will encourage the investigators who are studying the biology and diseases of the lymphatic system to collaborate, and work with them to create a virtual research network; **d.** The NHLBI, NIBIB, and NCI support development of techniques for molecular and functional imaging of the lymphatic system; **e.** The CCLR will look for opportunities to develop interdisciplinary training programs to train the next generation of scientists in this field; **f.** The NHLBI is in communication with investigators about establishing a tissue bank associated with the National Lymphatic Disease and Lymphedema Registry; **g.** Recently, NICHD Intramural investigators demonstrated that the zebrafish possesses a lymphatic system that shares many of the characteristics of the lymphatic vessels found in other vertebrates. The zebrafish is a powerful new model for studying lymphatic development and disease and for performing genetic screens to identify mutations responsible for lymphatic disease. This model will facilitate discovery of important information on the development and function of the lymphatic system; **h.** The NHLBI is supporting translational research seeking biomarkers to enhance the diagnosis and treatment of acquired lymphedema, which is frequently underdiagnosed or misdiagnosed, and will continue to look for opportunities to support research on biomarker discovery and development that aid diagnosis and management of lymphatic diseases.

#### Item

***Mitochondrial Disease and Dysfunction-*** The committee supports the effort to make greater progress in researching mitochondrial disease and dysfunction, and believes that the Director should therefore continue to prioritize research on functional variations in mitochondria under the Transformative Research grants program and other Common Fund activities. In light of the large number of NIH Institutes and Centers that have some involvement in mitochondrial-related research, the Committee urges the Director to enhance efforts to coordinate and promote such research. (p. 124)

#### Action taken or to be taken

NIH is committed to investigating mitochondrial disease and dysfunction, and is supporting this research through a combination of a robust investigator-initiated portfolio and solicitations that encourage research in specific areas where research gaps have been identified. NIH funded approximately 3000 grants totaling just under \$900 million in FY 2010 that were identified as mitochondrial research by using the search term “mitochondria” in the publicly available search tool, RePORTER. These grants represent a broad array of science that address mitochondrial function in many tissues and diseases, including cancer, aging, neurodegenerative diseases, diabetes, heart disease, hearing loss, fetal and childhood development, and basic cell biology.

For example, the NICHD supports a variety of projects focused on mitochondrial genetics and function, bioenergetics, and translational medicine. Specifically, the NICHD sponsors grants in several mitochondrial disorders with neurological impairment including Leigh syndrome, MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes) syndrome, MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), Coenzyme Q deficiency and others. Many of these projects

involve multidisciplinary teams with a commitment to the understanding of mitochondrial disorders, and at least two grants are for mentored career development (K) awards for junior investigators to develop expertise in the field. In addition, translational and clinical projects aimed at developing therapeutic interventions for mitochondrial disease are underway, including a clinical trial of a compound with preliminary efficacy in an encephalopathic disorder, pyruvate dehydrogenase deficiency. This project is being organized in partnership with the North American Mitochondrial Disease Consortium, a rare disease consortium supported by the NINDS and ORDR with the support of the patient advocacy group, the United Mitochondrial Disease Foundation (UMDF).

Additionally, NIEHS is working to understand how the environment influences mitochondrial dysfunction associated with multiple diseases and plans to issue a Request for Applications to support research for the identification of Biomarkers for the Early Detection of Environmentally-Induced Mitochondrial Dysfunction. The NIEHS intramural program is investigating genetic defects and environmental toxins that disrupt mitochondrial DNA (mtDNA) replication and maintenance. Genetic defects of mtDNA replication are some of the most common causes of mitochondrial diseases.

The NHLBI also provides significant support to mitochondrial research. It launched a new effort in FY 2010 through a solicitation titled "The Role of Cardiomyocyte Mitochondria in Heart Disease: An Integrated Approach." It intends to provide up to \$16 million through FY 2014 to support 6 awards funded through this solicitation, as indicated in the Funding Opportunity Announcement (FOA).

Centralized support of mitochondrial function and dysfunction is provided through the NIH Common Fund. Programs within the Common Fund, including the Interdisciplinary Research program, the NIH Director's Pioneer Awards, and the Molecular Libraries and Imaging program, support research aimed at improving our understanding of the role of mitochondria in diseases such as diabetes, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and cancer. In addition, planning activities are currently underway to launch a Single Cell Analysis program in FY2012 to foster the development of new tools to probe the composition, activity, and function of molecules within a single cell. These tools are expected to facilitate analysis of mitochondrial variation between cells and the role that this plays in the variable presentation of symptoms associated with mitochondrial disorders. The Director will continue to work to coordinate and promote this new program and the conduct of mitochondrial disease research across NIH Institutes and Centers as appropriate.

#### Item

**National Children's Study** - The Committee includes bill language providing \$194,400,000 for continuation of the National Children's Study (NCS). The Committee appreciates the improvements to the management and oversight of this study that have occurred in the past year. While the implementation of the main study has been delayed, the Committee believes this will allow more time to evaluate the project's scope and cost, and allow the NIH and Congress to make better-informed decisions about its future. (p.120)

#### Action taken or to be taken

Led by the NICHD, the National Children's Study (NCS) is a collaborative effort of the NIH, the CDC, the EPA, and other federal partners. The NCS would be the largest long-term examination of children's health ever conducted in the United States, following 100,000 children from before birth to age 21. When fully implemented, it will become a unique resource to advance understanding of the many factors in a child's environment and individual biological makeup that may influence child health and development over time.

In late 2009, the overall management of the study was changed, and program operations were modified to achieve cost savings. The timeline for the NCS was also modified to reflect approximately one year's delay in implementation of the "Main Study" due to the less than robust recruitment experience of the seven original Vanguard Centers. Currently, the study is in an expanded pilot ("Vanguard") phase. Three additional recruitment strategies have been developed through extensive literature searches and garnering expertise from other large studies: enhanced household, provider-based, and two-tiered (low-intensity, high-intensity) recruitment. Women who become pregnant within the next few years and who live in a study area may be eligible to participate. Each strategy is currently being tested in 10 additional NCS geographic areas. A total of 37 sites across the country are now participating in the expanded Vanguard phase of the study.

The Vanguard Study will evaluate the feasibility, acceptability, and cost of recruitment and perform formative research to inform the strategies and approaches that might be used in the Main Study. During the next year, NCS professional staff, advisory boards and other experts will continuously review and, as needed, refine the Main Study protocol. By summer 2011, information gathered from the Vanguard Study will permit evidence-based recommendations and cost estimates for the initial phase of the Main Study. When the protocol and the revised funding plan have been refined, they will be submitted for policy and regulatory review. If approved, the launch of the Main Study would be anticipated in the second half of FY 2012.

#### Item

***Neurodegeneration with Brain Iron Accumulation (NBIA)*** - The Committee urges the NINDS, NICHD, NEI and ORDR to put a higher priority on research involving NBIA, a group of rare disorders for which there is no treatment or cure. (p. 124)

#### Action taken or to be taken

The NIH; including NINDS, NICHD, NEI, and ORDR, support research on NBIA and other iron-related disorders to understand their causes and to identify new targets for therapeutic intervention. For example, previous research with support from NICHD and NEI has shown that many people with a type of NBIA disorder known as infantile neuroaxonal dystrophy (INAD) have mutations in a gene called PLA2G6. These mutations impair cells' ability to break down and use certain fats that are important for the maintenance of cell membranes, but little is known about how they lead to INAD. A

study supported by NINDS with funds from the American Recovery and Reinvestment Act focuses on how such mutations contribute to iron accumulation in an animal model of INAD. The findings from this research may suggest new routes to treatments for NBIA disorders. In addition to NBIA, impaired iron regulation has been associated with neurodegeneration in other diseases, including other types of childhood neurodegenerative disorders as well as Alzheimer's disease, Parkinson's disease, and retinal degeneration. Research supported and conducted by NIH in these areas is also yielding insights into understanding and treating NBIA. For example, the NICHD intramural division includes a section that studies the regulation of iron metabolism and iron-related neurodegeneration, and NEI supports efforts to understand iron regulation in the retina, which may provide insights into NBIA disease mechanisms in the eye. The NEI also has a large portfolio of grants aimed at developing treatments for retinal degeneration and optic atrophy. Therapeutic candidates identified through this research may apply to NBIA.

Beyond direct support for research projects, NIH also sponsors scientific conferences on NBIA and related disorders. Most recently, NINDS, ORDR, and NICHD sponsored "Brain, Blood and Iron: Joint International Symposium on Neuroacanthocytosis (NA) and Neurodegeneration with Brain Iron Accumulation (NBIA)," held in October 2010. Scientists from across the country, including NIH intramural researchers, provided the latest research findings and their implications for human health, such as whether the loss of certain proteins that regulate iron in the bloodstream causes adult-onset neurodegeneration and anemias. The broad objectives of the meeting were to define research priorities and resource needs, to promote interest and collaborations among researchers in related fields, and to attract new, early-career stage investigators to NA and NBIA research, all of which should stimulate new research to understand, diagnose, and treat these disorders.

#### Item

**Neurofibromatosis (NF)** - The Committee continues to place a high priority on NF and requests an update in the fiscal year 2012 congressional budget justification on the research being supported by the multiple NIH Institutes with an interest in this disease. (p. 124)

#### Action Taken or to be Taken

NCI-funded extramural and intramural investigators are carrying out studies that can provide important knowledge for preventing NF tumor recurrence, improving prognosis, and enabling therapeutics development. NCI's basic research program includes grants that investigate the function of the NF1 or NF2 tumor suppressor genes, their protein products, and the consequences of their inactivation. One project is examining a new and not yet recognized activity of the NF1 protein, Neurofibromin, to define the specific workings of the NF1 pathway and discover the most critical points to target therapeutically. Another project is investigating the molecular function of the NF2 protein, Merlin, and its interaction with the ErbB receptors, which have also been implicated in human cancers, to further understand the molecular basis of NF2.

NCI-funded researchers are generating and studying genetically-engineered animal models to assess the early cellular events triggering NF-associated tumors and define the tumor initiating cells. For example, a NCI-sponsored project is focusing on key enzymes that regulate cell communication downstream of Ras that are triggered following the loss of NF1 gene. Another project has developed a mouse model to mimic the origin of human cancer in NF disease, demonstrating that nerve stem cells are the cells that form tumor. The NCI intramural research program developed a light emitting system to enable the detection of spontaneous tumors as they evolve at early stages of the disease, which will be invaluable for use in preclinical studies of potential therapeutics. NCI intramural researchers are applying computerized skin examination techniques to measure accurately the growth with time of neurofibromas and other abnormalities on the skin in NF1 patients and in cancers with skin symptoms.

NCI's Children's Oncology Group (COG) and the intramural Pediatric Oncology Branch (POB) are currently conducting NF clinical trials. The Pediatric Brain Tumor Consortium and the COG Phase 1 Consortium completed phase 1 studies of lenalidomide in pediatric brain tumors and pediatric solid tumors, respectively. The COG is now developing a phase 2 study of lenalidomide in children with low-grade gliomas. The POB is coordinating a number of trials for children and young adults with NF1 and neurofibromas, such as a multi-institutional trial for the treatment of sporadic and NF1-related nerve connective tissue tumors with chemotherapy and a phase 1 trial of satraplatin, a drug that has demonstrated antitumor activity in preclinical testing models.

NICHHD provides ongoing support for four Learning Disabilities Research Centers that include an emphasis on understanding the origins of learning disabilities that may have an impact on reading, writing, and oral language development. In collaboration with the NCI, NICHHD intramural scientists are studying the growth and development of children with NF, their responses to novel treatments for their multiple tumors, and the molecular causes of some of the rare tumors associated with NF.

NINDS also supports a broad NF research portfolio. One NINDS-funded study is using behavioral and fMRI imaging methods to determine the best interventions for improving reading disabilities in children with NF1. NINDS also supports studies in animal models, to understand how NF gene mutations affect cellular mechanisms important for learning and memory. Spinal cord injury does not occur at an increased rate in NF, but patients do have a higher incidence of bone abnormalities, such as scoliosis. NINDS supports a project to better characterize bone abnormalities in NF1, to identify genetic profiles associated with these abnormalities, and to assess health quality of life in children and adolescents with NF1 and scoliosis. Another study investigating the clinical history of spinal abnormalities in children with NF1 is also investigating whether radiographic screening tools may help predict the development scoliosis. As part of a research center focused on the molecular genetics of inherited neurological tumor syndromes, NINDS also funds a patient database for genotype/phenotype analysis and a tissue bank that collects and maintains tissue from patients with NF2 as well as other nervous system tumor syndromes. Researchers have used these resources to identify genetic changes

and signaling pathways involved in the initiation and progression of neurological tumors, and future studies will continue to examine the mechanisms of tumorigenesis.

NF2 affects hearing and balance and occurs in about one out of every 40,000 Americans. A mutation of the NF2 tumor-suppressor gene on chromosome 22 is strongly associated with bilateral nerve tumors called vestibular schwannomas, which can cause hearing and balance disorders. NIDCD supports research that explores how proteins involved with the NF2 mutation may be used to test and develop molecular and drug therapies for NF2 disorders, and to develop auditory prostheses for brainstem and higher levels above the auditory/vestibular nerve for patients who have lost that nerve function from NF2 or surgical removal. NIDCD is providing auditory and vestibular testing and neuro-otologic evaluation and services for a natural history study of NF2 patients led by NINDS intramural investigators.

NHLBI is supporting a project investigating how the causative gene for NF1 affects cardiac diseases and another project exploring the gene's role in myeloproliferative disease. NHLBI-supported research is also investigating other syndromes that involve the Ras-MAPK signaling pathway, including two focused on a form of leukemia that is associated with NF1. An NHLBI-supported investigator in collaboration with an NINDS-supported investigator and the NIH Clinical and Translational Science Awards program has reported evidence of vascular inflammation in a mouse model of NF1 vasculopathy.

#### Item

**Neurogenic Bladder** - The Committee encourages the NIDDK, NICHD and NINDS to study the causes and care of the neurogenic bladder in order to improve the quality of life of children and adults with spina bifida; to support research to address issues related to the treatment and management of spina bifida and associated secondary conditions, such as hydrocephalus; and to invest in understanding the myriad co-morbid conditions experienced by children with spina bifida, including those associated with both paralysis and developmental delay. (p.124,125)

#### Action taken or to be taken

NICHD is committed to research efforts on the prevention and treatment of spina bifida, one of a group of structural birth defects known as neural tube defects (NTDs), in which the neural tube does not completely close during pregnancy. Infants born with spina bifida have significant disruptions in the brain and spinal cord. Although surgery to close the neural tube can be performed, NTDs generally lead to permanent damage to the spinal cord.

NICHD's ongoing multicenter network trial, the Management of Myelomeningocele Study (MOMS), is evaluating the relative safety and efficacy of fetal surgical repair and traditional postnatal repair of open NTDs. Women whose fetuses are diagnosed with spina bifida midway through their pregnancy are enrolled in a rigorous protocol at one of three clinical sites, the only sites in the U.S. offering fetal surgical repair. They are randomized to receive either prenatal surgery on the woman and the fetus, or to return at the end of the pregnancy to undergo standard closure by the same surgical teams.

Three-year follow-up of all 200 study patients will occur to evaluate the effects on maternal health, fetal outcomes, and neonatal and infant treatment needs for orthopedic and urologic problems common to people with spina bifida, and early childhood neurologic and cognitive functioning. Nearly all of the participants have been enrolled in this study. NICHD also has provided supplemental funding to the MOMS trial to assess the impact of *in utero* surgery on urologic outcomes as compared to standard postnatal repair.

NICHD supports other basic, translational, and clinical research on spina bifida including sensorimotor development and amelioration of deficits by exercise, cognitive development, and physical and psychosocial co-morbidities. Among the projects in NICHD's special birth defects initiative are family-based studies to identify genetic variants that influence the risk of spina bifida and other studies targeting potential nutritional and environmental influences. Folate supplementation helps to prevent the occurrence of some NTDs, but the mechanism of folate action needs to be clarified, since a proportion of NTDs are folate-resistant. To target the causes of the folate-resistant NTDs, researchers must be able to understand the underlying mechanisms of normal neural tube formation. Maternal diabetes and obesity both are associated with increased risk of NTDs, and a new NICHD-supported study implicates high blood sugar (hyperglycemia) as a factor that can contribute to NTDs. Together, these studies will help provide a clearer picture of the causes of NTDs and allow us to develop more efficient prevention strategies. NINDS also supports research on the causes of spina bifida. Some children with spina bifida develop hydrocephalus, and NINDS is supporting a study on behavioral and cognitive outcomes in children treated for this condition with shunts to remove excess cerebrospinal fluid.

In addition, NIDDK recognizes that spina bifida is the most common cause of pediatric neurogenic bladder. NIDDK continues to support research into normal and abnormal nervous system-based bladder function, and bladder tissue regenerative work, through individual grants and through the newly established Planning Centers for Interdisciplinary Research in Benign Urology. This research may lead to quality-of-life improvements for patients with this condition.

#### Item

***Overlapping Chronic Pain Disorders*** - The Committee again notes the growing body of evidence demonstrating considerable overlap among chronic fatigue syndrome, endometriosis, fibromyalgia, headache, interstitial cystitis, irritable bowel syndrome, temporomandibular joint and muscle disorders, and vulvodynia. These poorly understood and neglected conditions impact millions of Americans and cost the Nation tens of billions of dollars each year. The Committee requested last year that the Director coordinate a trans-NIH research initiative, and the NIH responded that this work would be carried out by the Trans-NIH Working Group for Research of Chronic Fatigue Syndrome [CFSWG]. The Committee is not satisfied with that response, as the scope of the proposed initiative spans well beyond the purview of the CFSWG, and strongly urges the NIH to take a more comprehensive approach to these conditions. The Committee urges the NIH to promptly develop and coordinate, with all relevant ICs, a

trans-Institute research initiative to support studies aimed at identifying etiological pathways of these overlapping conditions with the goal of identifying potential therapeutic targets. (p.125)

#### Action taken or to be taken

The NIH recognizes the continued interest and concern of the Committee regarding overlapping chronic pain disorders, many of which disproportionately affect women, and all of which adversely affect the quality of life of millions of Americans. In recent years, catalyzed by the NIH Pain Consortium, NIH has launched a number of trans-NIH Initiatives focused on pain, including chronic pain. For example, the Transformative Research Projects (T-R01) Awards Program, funded through the Common Fund, highlighted the transition from acute to chronic pain as an area of interest. The Pain Consortium, through the NINR, issued a series of funding opportunity announcements (FOAs) intended to stimulate and foster a wide range of basic, clinical, and translational studies on pain, especially those conducted by interdisciplinary and multidisciplinary research teams. Supported through the American Recovery and Reinvestment Act (ARRA), the NIH Challenge Grants and Grand Opportunity initiatives both included several pain topics as targeted areas in an effort to quickly expand the NIH pain research portfolio. The NIH Neuroscience Blueprint launched a five-year pain research initiative in 2010 investigating the neural basis of chronic pain disorders. The NIH anticipates further elucidation of specific opportunities in overlapping chronic pain conditions through a contract with the Institute of Medicine to convene a "Conference on Pain" to develop recommendations on how to significantly improve the state of pain research, assessment, diagnosis, treatment, and management. All of these trans-NIH efforts should enhance our understanding of the underlying pathways that affect the overlapping chronic conditions named by the Committee.

Pain research, including research on overlapping chronic pain disorders, is a crosscutting issue at the NIH that spans the missions of multiple Institutes and Centers (ICs). In 2008, NIH worked with the TMJ Association to convene a critical meeting to discuss possible common genetic factors and mechanistic pathways that link these co-morbidities, accounting for their co-occurrence in patients. The NINDS is supporting a ten-year study on overlapping pain conditions that mainly affect women, to identify factors that influence pain amplification in five complex persistent pain disorders. The NIDCR convened a two-day workshop to assess the next steps in leveraging the explosion in genetic information and technology in order to move forward with research on the genetics of temporomandibular joint disorders and related chronic pain conditions. The NINR intramural research program conducts genetic and proteomic research to examine the cellular mechanisms underlying pain symptoms in order to investigate therapeutics for chronic pain disorders. NINR also sponsored a "Pain Bootcamp" in 2010 designed to train scientists in state-of-the-art methodologies used in pain research. NIDA recently funded a series of projects under an initiative to examine central nervous system intersections of chronic pain, analgesia, and drug addiction. NCCAM and NIA sponsored an initiative to examine the mechanisms and management of chronic pain in older adults. The CFSWG, managed by the Office of Research on Women's Health, developed an FOA to explore the causes and treatment of chronic

fatigue syndrome (CFS), an initiative which also addresses overlapping chronic pain disorders that are co-morbid with CFS. The CFSWG is also sponsoring a State of the Knowledge Meeting on CFS in 2011 that will inform new initiatives that could include co-morbid pain conditions. In addition, the NICHD is planning to convene a conference on vulvodynia in the summer of 2011. Such activities, led by the ICs and enhanced by the collaborative and interdisciplinary efforts of the Pain Consortium, are intended to promote interactions among investigators in the field of pain research, in order to build a vibrant scientific community that would respond to and help shape future funding opportunities related to chronic pain disorders.

#### Item

**Pain** - The Committee applauds the NIH for entering into negotiations with the Institute of Medicine to convene a "Conference on Pain" to develop recommendations on how to significantly improve the state of pain research, assessment, diagnosis, treatment, and management, as authorized by the Patient Protection and Affordable Care Act [PPACA). The Committee urges the NIH to assure that appropriate attention is given to chronic pain conditions that solely or disproportionately impact women, including chronic fatigue syndrome, endometriosis, fibromyalgia, interstitial cystitis, temporomandibular disorders, and vulvodynia. The Committee also urges the NIH to promptly appoint and convene a new Interagency Pain Research Coordinating Committee, as described in the PPACA. This committee will provide important visibility to existing efforts, help identify critical research gaps in this field, stimulate pain research collaboration with other Government agencies such as the Departments of Defense and Veterans Affairs, and provide an important avenue for extramural stakeholder involvement as the pain research agenda evolves. (p.125)

#### Action Taken or to be Taken

The NIH appreciates the Committee's recognition of our efforts to respond quickly to the pain-related provisions of the Affordable Care Act (ACA). We completed negotiations with the Institute of Medicine (IOM) to convene a "Conference on Pain," a task that has been added to a task order contract between NIH and the National Academies. The goal of this Conference is to develop recommendations to improve the state of pain research, assessment, diagnosis, treatment, and management. The IOM is currently assembling a committee of experts on pain research, pain care, and education that will hold four meetings in addition to the Conference over the next eight months. A report of the findings will then be delivered to Congress as mandated by the ACA. As reflected in the pain care provisions of the Act, the issues surrounding pain care, research, and education are broad, far reaching, and complex. We anticipate that the Conference findings will provide insight to a number of Federal agencies grappling with these important issues. We have encouraged the IOM to pay appropriate attention to chronic pain conditions and to "identify demographic groups and special populations that may be disparately under-treated for pain." We further conveyed to the IOM that this effort should also address chronic pain conditions that solely or disproportionately impact women.

The Interagency Pain Research Coordinating Committee (IPRCC) was chartered by the HHS Secretary in July 2010, and a Federal Register Notice establishing the Committee was published July 15, 2010. The NIH published a request for nominations in the Federal Register in the fall of 2010 and submitted a draft slate of members to the Department. NIH will invite participation from other relevant Federal agencies, including the Department of Defense and the Department of Veterans Affairs. The HHS Secretary has the final authority to appoint members to this Committee. Once the appointments are made, the NIH will move quickly to hold the first Committee meeting. We expect the IPRCC to help accelerate efforts in pain research and promote collaboration across the government, with the ultimate goals of both improving pain-related treatment strategies and advancing our fundamental understanding of pain.

#### Item

**Palliative Care-** The Committee strongly urges the NIH to develop a trans-Institute strategy for increasing funded research in palliative care for persons living with chronic and advanced illness. Research is needed on: treatment of pain and common non-pain symptoms across all chronic disease categories, which should include cancer, heart, renal and liver failure, lung disease, Alzheimer's disease and related dementias; methods to improve communication about goals of care and treatment options between providers, patients, and caregivers; care models that maximize the likelihood that treatment delivered is consistent with patient wishes; and care models that improve coordination, transitions, caregiver support, and strengthen the likelihood of remaining at home. (p.125,126)

#### Action taken or to be taken

The NIH appreciates the Committee's recognition of the importance of improving palliative care for persons with chronic and advanced illness. Given the urgent need to enhance quality of life and health care for individuals with such conditions, including individuals at the end of life, NIH supports a number of activities to advance palliative care and end-of-life science across the lifespan and across a spectrum of diseases and conditions. Moreover, since palliative and end-of-life care are topics that span the missions of many of the NIH Institutes and Centers (ICs), multiple trans-NIH efforts are underway to advance the science in these areas. The NIH End-of-Life Palliative Care Special Interest Group provides a forum for interdisciplinary scientists across the NIH to exchange ideas related to palliative and end-of-life care. The National Institute on Drug Abuse (NIDA) and NIH Office of AIDS Research co-sponsored a meeting with the Clinton Foundation HIV/AIDS Initiative on increasing access to pain treatment and palliative care in resource-limited settings, while minimizing the risk of drug diversions. In addition, the NIH Common Fund and National Institute of Nursing Research (NINR), recently awarded \$7.1 million provided by the American Recovery and Reinvestment Act to support a Palliative Care Research Cooperative, a multi-institution effort to conduct collaborative research on palliative care, including a multi-site clinical trial focused on statin use in patients who are near death.

NINR, as the lead NIH IC for end-of-life research, has a major role in creating opportunities to build end-of-life and palliative care (EOL/PC) science. Within NINR, the

Office of Research on End-of-Life Science and Palliative Care, Investigator Training, and Education coordinates research, training, and educational efforts in EOL/PC science. Supported with funding from the NIH Office of the Director, NINR has also launched a major evaluation study to assess current and future needs in EOL/PC science across Federal and private research entities, an effort that will inform trans-NIH strategies in these areas. Finally, NINR recently published an informational brochure for the public entitled “Palliative Care: The Relief You Need When You’re Experiencing the Symptoms of Serious Illness” that explores the benefits of palliative care and answers common questions. The brochure has been downloaded over 750,000 times from the NINR website since its release.

Studies in EOL/PC science have produced many important results, including findings related to patient/family/provider communications and caregiver health. For example, one recent National Institute of Mental Health (NIMH) and National Cancer Institute (NCI)-supported study reported that caregivers of cancer patients who died in an intensive care unit were at higher risk of developing psychiatric illnesses during bereavement than caregivers of patients who died at home. An NINR-supported study reported that patients participating in the Physician Orders for Life-Sustaining Treatment (POLST) program, which is designed to better communicate patient preferences for end-of-life treatment to physicians, were less likely to receive unwanted life-sustaining treatments than patients with traditional Do-Not-Resuscitate orders. Other studies have explored interventions that effectively reduced stress in caregivers of family members with life-limiting illness, and organizational factors that influenced the quality of hospice care in assisted-living facilities. These are only a few examples of NIH-supported studies that are enhancing the knowledge base for palliative care science and that have the potential to significantly improve quality of life for individuals with chronic and advanced illness. NIH will continue its strong commitment to these areas of research in the coming years.

#### Item

**Psoriasis-** The Committee recognizes that additional genetics, immunology and clinical research focused on understanding the mechanisms of psoriasis and psoriatic arthritis are needed, and it encourages the NIAID and NIAMS to further study the genetic susceptibility of psoriasis; develop animal models of psoriasis; identify and examine immune cells and inflammatory processes involved in psoriasis; and elucidate psoriatic arthritis specific genes and other biomarkers. The Committee also recognizes the mounting evidence of co-morbidities associated with psoriasis and the 50 percent higher risk of mortality for people with severe psoriasis. The Committee urges the NHLBI to consider these factors in its research, specifically that individuals with severe psoriasis have an increased risk of heart attack, independent of other major risk factors such as hypertension, diabetes and obesity, and that for people in their 40s and 50s with severe psoriasis, the risk of heart attack is more pronounced. The Committee also urges the NIDDK and NIMH to consider in its research that diabetes and psychiatric symptoms are more prevalent for patients with severe psoriasis than for those with mild disease. (p.126)

#### Action taken or to be taken

NIH supports basic, translational, and clinical research on psoriasis, including psoriatic arthritis, which aims to better understand the roles of the immune system, genetics, epigenetics, and other factors in the development and progression of the disease and to develop new therapies. For example, the NIAMS continues to support a Center of Research Translation (CORT) where investigators are testing a novel photodynamic therapy for psoriasis, and exploring the role of specific proteins and cell subsets in the pathogenesis of the disease, using novel cell-based assays and animal models. Other NIAMS-supported researchers are examining gene expression in lesional psoriatic plaques, which are scaly areas of inflammation. The identification of genes and their products whose expression is altered in lesional psoriatic skin will lead to a better understanding of the pathogenic mechanisms of the disease, including inflammatory processes. Finally, NIAMS-supported researchers have recently determined that patients with psoriasis have an increased risk of depression, anxiety, and suicide. This information could aid in the development of targeted interventions that could significantly improve the quality of life of patients with psoriasis.

In collaboration with the NIDDK and the Juvenile Diabetes Research Foundation International, NIAID supports the Cooperative Study Group for Autoimmune Disease Prevention (CSGADP), which includes projects aimed at rapid development, from animal models to human studies, of surrogate markers for autoimmune disease progression and regulation. NIAID also supports clinical trial networks, such as the Autoimmunity Centers of Excellence and Immune Tolerance Network, which include studies on autoimmune diseases.

The inflammatory response associated with severe psoriasis is thought to contribute to an elevated rate of type 2 diabetes. The NIDDK recently tested an inexpensive generic anti-inflammatory medication in its Targeting Inflammation with Salsalate in Type 2 Diabetes clinical trial. The study found salsalate to be well tolerated and effective for lowering blood glucose and certain measures of risk for atherosclerosis. Based on these encouraging results, an expanded study of safety and efficacy is now ongoing in larger numbers of patients, with a longer duration of treatment. If the approach is successful, this research could offer a new therapy for diabetes, and might be particularly efficacious when diabetes develops in the setting of chronic inflammatory conditions, including psoriasis.

NHLBI is aware of the potential links between psoriasis and cardiovascular disease and, as such, is currently funding a study entitled “The Risk of Myocardial Infarction in Patients with Psoriasis.” NHLBI is funding several other projects that also address the link between psoriasis and cardiovascular disease, inflammation, and angiogenesis.

The NIMH Strategic Plan fosters innovative research that will lead to a greater understanding of the trajectory of mental disorders, including those co-morbid with other physical diseases and conditions. For example, NIMH supports a Funding Opportunity Announcement that encourages innovative intervention and services research. This

research is aimed at preventing or ameliorating mental disorders; the co-occurrence of mental, physical, and substance abuse problems; and the functional consequences of these problems across the lifespan.

#### Item

***Hematology (Regenerative Medicine)*** – The field of regenerative medicine represents a unique approach to treating diseases and disorders by enabling the body to repair, replace, restore, and regenerate damaged or diseased cells, tissues, and organs. The Committee believes that the NIH should carefully and deliberately consider how best to organize and undertake research in this promising field, with input from experts in multiple disciplines. The Committee urges the Director to develop a plan that would: assess current research; identify research gaps including research methodologies; develop a mechanism to allow for the coordination of research between Institutes; consider the development of a separate study section; and in coordination with the FDA, develop clinical trial methodologies and measures to assure the safety and efficacy of therapies, including data and sample registries. The Committee requests a response in the fiscal year 2012 congressional budget justification. (p. 126)

#### Action taken or to be taken

The NIH has invested an estimated \$818 million in regenerative medicine in FY 2010. An investment of this size reflects regenerative medicine's relevance to a wide range of science, including bioengineering and materials science, stem cell science, and translational and clinical aspects of regenerative medicine. Regenerative medicine is an interdisciplinary field, drawing on resources beyond the NIH. The efforts of the Multi-Agency Tissue Engineering Science (MATES) Working Group have fostered trans-agency programs to enhance many aspects of regenerative medicine. To improve coordination of research opportunities and speed the translation of basic findings into cellular therapies, the NIH Director, acting through DPCPSI and the Common Fund, held a workshop on translational opportunities for stem cells in January of 2010. Participants identified research gaps and barriers, including research methodologies, which hinder the development of new stem cell therapies. Input from the workshop, coupled with an assessment of the current state of regenerative medicine research, led to the establishment of the NIH Center for Regenerative Medicine (NCRM) through the Common Fund. In order to build an intramural community of expertise in stem cell research the Center funded eleven intramural stem cell projects during FY2010.

This Center is to be housed within the NIH Intramural Program and will facilitate the coordination of research between Institutes by serving as a central resource for extramural and intramural investigators. Candidates for the Director are currently being interviewed. The NCRM will develop methodologies and technologies necessary for clinical applications and will generate a bank of well-characterized, diverse stem cell lines. NCRM will collaborate with extramural and intramural investigators to develop novel therapeutic approaches for defined diseases/conditions using patient-derived induced pluripotent (iPS) cells, human embryonic stem cells (hESCs), and adult stem cells, as appropriate. NCRM will continue to investigate the therapeutic potential of different types of stem cells, the control of stem cell integration into functional tissues for

transplants, and the use of stem cells as surrogates for human responses in vitro. Areas that are particularly suitable for stem cell therapies, such as hematologic disorders, ocular diseases, liver failure, and bone regeneration, are likely to be early targets for NCRM. Ultimately, cells for use in patients will be manufactured according to FDA regulations and Good Manufacturing Practice (GMP) guidance.

Recognizing a need to develop novel clinical trial methodologies and measures to ensure safety and efficacy of therapies, the NIH and FDA initiated a new program in Regulatory Science in FY 2010. This program, funded by both the NIH Common Fund and the FDA, is intended to generate new and improved methods for clinical trials and for assessing safety and efficacy of therapeutics. While the specific research to be supported through this program will be guided by ongoing activities of the newly formed NIH-FDA Joint Leadership Committee, one area of research that could be addressed is the development of clinical trial methodologies for cell therapies used in regenerative medicine.

While the NCRM program will be a central core providing research resources for the entire community the majority of regenerative medicine research will continue to be supported by the ICs. The breadth of scientific methodologies and disciplines encompassed in the field of regenerative medicine as well as the diversity of organ systems that are addressed in individual projects means that no one group of experts is capable of reviewing the science. As such, the science will continue to be reviewed by the study section most closely aligned with the science of each application, and the NIH will continue its efforts to insure appropriate balance and expertise exists in the key review groups.

#### Item

**Sex Differences** - The Committee urges the NIH to put a higher priority on understanding the basic biology of the impact of sex gender in development, diagnosis, and treatment of disease. Topics should include the cellular and molecular basis of sex differences in the natural history of development of and treatment for disease; a clearer definition of the impact of the hormonal milieu on risk and progression of diseases in women; and an integrated approach to understanding how neurological/physiological factors impact development of disease in women. The Committee recommends that study sections should be better equipped to evaluate such proposals of sex differences in disease, as these typically are complex integrated physiological problems requiring a multidisciplinary approach. The Committee requests an update on these efforts in the fiscal year 2012 congressional budget justification. (p. 126)

#### Action taken or to be taken

The *Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCOR)* program of the NIH Office of Research on Women's Health (ORWH) represents an excellent model for stimulating research on sex differences from the cellular and molecular level to translational and clinical research for women with significant clinical applications to gender-specific human health. Each SCOR has a central theme capturing an important issue in sex/gender factors in a priority women's

health issue and provides a mutually supportive interaction between basic scientists and clinical investigators.

Currently, the SCOR program consists of 11 centers that compare sex and gender contributions to health and disease and includes interdisciplinary research on pregnancy, substance abuse, the urinary tract, depression, osteoporosis, and pain. Each SCOR has a minimum of three interdisciplinary research projects, representing both basic and clinical research. The basic science core addresses the cellular and molecular basis of sex differences in the natural history of development of and treatment for disease and each SCOR develops a research plan bridging basic and clinical research on sex/gender factors underlying health issues that affect women.

ORWH has introduced a new strategic plan for women's health research. One of the major priorities of the new strategic plan is to expand sex differences research to encompass basic science as well as clinical research. The NIH is especially interested in fostering research in women's health in the high priority areas of prevention, diagnosis and treatment, and the biological, behavioral, cellular, and molecular basis of sex and gender differences. ORWH intends to stimulate and encourage the exploration of biological sex differences at multiple levels, from genes to hormones to complex biological systems. The contributions of biological sex and social parameters of gender can assist in understanding the diversity of health outcomes and this knowledge can be applied in the development of the next generation of interventions and medical treatments.

At the NIH, grant applications are evaluated through a peer review process that is fair, timely, and conducted in a manner free of bias. Study sections are required to have appropriate expert representation depending on the scientific areas reviewed and diversity of reviewers. The NIH is interested in receiving nominations for reviewers from professional groups and would welcome nominations from the scientific community whose expertise is on clinical and basic studies that include the influence of gender on disease. NIH also monitors the representation of women on study sections and as study section Chairs. At present, the percentage of women serving on study sections exceed the percentage of female grant applicants to NIH.

#### Item

***Spinal Muscular Atrophy Carrier Screening*** - The Committee continues to strongly support the development of a panethnic carrier screening program for SMA. While the Committee is very pleased that in October 2009 the NHGRI, NICHD, and NINDS collectively sponsored a meeting of representatives from government, academia, professional societies, advocacy groups, and industry to explore the scientific basis for SMA carrier screening, many challenges remain to implementing a comprehensive panethnic carrier screening protocol for SMA. The Committee is particularly concerned that contradicting recommendations from professional societies and inconsistencies between various industry-published educational materials for SMA carrier screening are creating confusion among professionals and the public. The Committee strongly encourages the NHGRI, NICHD, and NINDS to collaborate with stakeholder groups to

develop unified, specific, and consistent recommendations, guidelines, and educational materials for providers and patients. Additionally, the Committee urges the NIH to collaborate with stakeholders and relevant government entities to address gaps in federal policy relative to carrier screening. (p. 126,127)

Action taken or to be taken

As the appropriate professional organizations continue to work through their evaluations of the evidence to make recommendations on carrier screening, NIH will continue to participate in stakeholder discussions on the science and public health issues intrinsic to carrier screening programs. Recognizing that clinical practice guidelines are the remit of the clinical organizations, NIH will facilitate discussions as appropriate to support the Federal role in evidence collection and evaluation in order to inform the development of clinical guidelines for carrier screening programs. With regard to addressing gaps in Federal policy, the findings of the October 2009 meeting were presented to both the Advisory Committee on Heritable Diseases in Newborns and Children (ACHDNC), and the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). NHGRI, NICHD, and NINDS will continue to work with ACHDNC, providing technical expertise where necessary. ACHDNC has formed a taskforce to "engage a multidisciplinary stakeholder group about perspectives on public health, personal health, and health care system readiness and needs for expanded population-based carrier screening for genetic conditions," with a view to having recommendations ready to submit to the Secretary of HHS by mid-2012. NHGRI and NICHD also will continue to collaborate with other NIH Institutes and Centers on activities related to research or to the development of educational materials on carrier screening, not only for SMA, but also for other autosomal recessive disorders (e.g., sickle cell disease).

Item

**Stroke in Women** - The Committee encourages the ORWH to support research to determine the biologic basis, including studies of genetic susceptibility factors, as to why brain aneurysms are much more frequent in women compared to men, particularly at younger ages, and initiatives to advance the understanding of stroke care in women, including poststroke rehabilitation, and the identification of stroke treatment and rehabilitation. (p.120)

Action taken or to be taken:

The Office of Research on Women's Health (ORWH) partners with Institutes and Centers across the NIH to support meritorious research, including stroke in women. To further advance biomedical science for women's health and sex differences research, the ORWH recently coordinated an NIH-wide strategic planning process; the main document is entitled, *Moving into the Future With New Dimensions and Strategies: A Vision for 2020 for Women's Health Research* (NIH publication No. 10-7606). This plan was released to the public on September 27, 2010. Several areas of the strategic plan that have direct relevance to this topic include research on the life span of girls and women, vascular biology, blood flow and brain imaging, and the importance of sex differences research in basic science studies. This plan can be used to stimulate research, including studies on the development and application of new technologies, to

improve the detection, diagnosis and treatment of stroke in women, especially in young women.

In addition to advancing the science underlying women's health research, ORWH has created an on-going investigator-initiated grant mechanism entitled, Advancing Novel Science in Women's Health Research (ANSWHR), a program announcement (PA) that has 23 NIH institute and center (IC) partners (PAS-10-226). This PA is available for extramural investigators interested in studying the specific questions identified by the Committee. ORWH and its IC partners look forward to providing grant funding to those projects receiving meritorious scientific reviews.

#### Item

***Tuberous Sclerosis Complex (TSC)***-The Committee applauds the research funded to date by the NIH that has led to a better understanding of TSC and its multiple manifestations. The Committee encourages the Office of the Director to launch a new, multi-Institute approach focused on translational research that will lead to the identification of new drug targets and new treatments for individuals with TSC. In addition, since TSC is a gateway into understanding autism spectrum disorder, the Committee encourages NIH to support research in this area. (p. 127)

#### Action taken or to be taken

While many NIH institutes support translational research through their own mission-specific programs, a trans-NIH effort of 16 NIH institutes and centers that support neuroscience research through the NIH Blueprint for Neuroscience Research, recently launched a new translational research effort, the Neurotherapeutics Grand Challenge, to help identify new drug targets and treatments for neurological disease. This multi-institute initiative encourages proposals for the development of novel drugs for all neurological disorders, including TSC.

NIH-funded research has shown the "gateway" potential of TSC and its underlying molecular pathways in understanding a variety of biological conditions and diseases. The National Institute of Neurological Disorders and Stroke (NINDS) supports research exploring the effects of the mutations in the TSC1 and TSC2 genes and the genes' molecular signaling pathways in developmental changes in brain structure and the regulation of connections between nerve cells. The NINDS also funds research to determine mechanisms of epileptogenesis in TSC, one of the most common causes of epilepsy, and to develop possible therapeutic approaches. To understand the link between TSC and autism, the NINDS supports a project using Recovery Act funds to identify proteins that interact with proteins encoded by genes associated with autism. The researchers have found that central to many of these interactions are TSC1 and TSC2 proteins, and they are now working to develop and characterize animal models to understand better these protein interactions. The NINDS also continues to support research on tumor development and treatment, much of which may be relevant to treating tumors in TSC patients.

The National Cancer Institute (NCI) continues to support research investigating the molecular and cellular basis of TSC and the underlying signaling pathways. Recent studies have highlighted potential new targets for diagnosis and treatment of TSC, among a variety of human cancers. One study showed, for example, that loss of TSC1 and TSC2 proteins causes incorrect localization of certain proteins due to a defect in cellular structure, while another study indicated that tumor formation associated with TSC may be caused by an imbalance between cell proliferation and death, due to defects in the TSC1 and TSC2 genes.

The National Heart, Lung, and Blood Institute (NHLBI) supports research on lymphangioleiomyomatosis (LAM), one of the manifestations of TSC gene dysfunction. LAM is a progressive, rare lung disease that almost exclusively affects young women. It occurs both in patients who have TSC and also sporadically (i.e., as an isolated disorder). Research under way includes development of a LAM Genome Atlas, research to understand the ability of LAM cells to metastasize, and determination of the role of estrogens in this disease. These and other projects seek to find additional treatment targets, identify molecular markers, and determine the mechanisms of lung destruction. The NHLBI supports collection, processing, and distribution of LAM tissue as well as development of a public use data set through the National Disease Research Interchange. The Institute continues to co-fund the annual LAM scientific conference.

#### Item

**Vulvodynia** - The Committee notes the lack of resources allocated to the vulvodynia educational campaign in fiscal years 2009 and 2010, and it urges the Director to reinvigorate this initiative by allocating sufficient resources to expanding the scope of this important effort. Developed educational materials should be widely disseminated to federally funded health centers and college health clinics, as well as to the public, patient and medical communities. In addition, the Committee requests that the ORWH support a vulvodynia conference to be held in fiscal year 2011. (p.121)

#### Action taken or to be taken

The Office of Research on Women's Health (ORWH), in partnership with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), has continued to publicize the Vulvodynia Awareness Campaign, in both FY 2009 and FY 2010 via the main ORWH website (<http://orwh.od.nih.gov/health/vulvodynia.html>). Additionally, ORWH highlights Vulvodynia by distributing information at community events and exhibits. Planning is underway between ORWH and the National Library of Medicine (NLM) to expand the Vulvodynia Awareness Campaign using the Women's Health Resources Web Portal, (<http://sis.nlm.nih.gov/outreach/whrhhome.html>). Through the use of the Web Portal, user groups (researchers, consumers, advocates, etc.) will engage in online activities using social media tools such as Facebook, Twitter, bookmark sharing programs, and other tools to highlight and create awareness of Vulvodynia and pelvic pain information at NIH and across the Department of Health and Human Services. The NICHD Clearinghouse remains the distribution point for the Vulvodynia Information Kits and individual Fact Sheets that are part of the Vulvodynia

Awareness Campaign, as well as the ORWH facilitation of materials through its own channels and community outreach.

In FY 2011, ORWH and NICHD will jointly hold an invitational scientific meeting in Bethesda, MD. To assist more broadly for investigator-initiated research applications, and to provide technical assistance to prospective applicants planning to submit research applications in response to the three vulvodynia Funding Opportunity Announcements (FOAs), the NICHD convened a pre-application workshop, with ORWH staff in attendance. Nineteen registrants attended the internet-assisted workshop on August 13, 2010. Meeting information and PowerPoint slide presentations are available on the NICHD Web Site for viewing by investigators interested in submitting grant applications in response to the vulvodynia FOAs, R01, R03, R21:

<http://grants.nih.gov/grants/guide/pa-files/PAR-10-190.html>

<http://grants.nih.gov/grants/guide/pa-files/PAR-10-191.html>

<http://grants.nih.gov/grants/guide/pa-files/PAR-10-192.html>