***Eunice Kennedy Shriver* National Institute of Child Health and Human Development**
Division of Intramural Research
BOARD OF SCIENTIFIC COUNSELORS
MINUTES
June 1, 2018
Building 31, Room 2A48

Members Present: Dr. Scott A. Rivkees (chair), Dr. Kate Ackerman (nominee), Dr. Vanessa Auld (nominee), Dr. Elizabeth Bonney (nominee), Dr. Jeanne Brooks-Gunn, Dr. Serdar Bulun, Dr. Frances Jensen, Dr. Deborah L. Johnson (nominee), Dr. Kojo A. Mensa-Wilmot, Dr. Antonios Mikos, Dr. Yoel Sadovsky, Dr. Susan S. Taylor, Dr. Eric Vilain, and Dr. Martha Werler (nominee).

Federal Employees Present: Dr. Constantine A. Stratakis, Dr. Charles Dearolf, Ms. Francie Kitzmiller, and at various times additional members of the NICHD staff participated in the meeting.

I. OPEN SESSION

The meeting convened at 8:03 a.m. Dr. Stratakis welcomed everyone. He thanked outing members, Dr. Jeanne Brooks-Gunn and Dr. Antonios Mikos, for their years of service on the BSC and Dr. Bianchi presented certificates to the outgoing members.

Dr. Stratakis introduced Dr. Diana Bianchi, Director, NICHD, to provide the Director's Report.

Director's Report

Dr. Bianchi provided an outline of her talk which included budget updates, the strategic planning process, the trans-NIH pediatric research consortium, progress towards inclusion, and staff updates.

The NIH appropriation has increased $2B in each of the two previous fiscal years and by $3B in FY18 to just over $37B. Based on the President's budget request NICHD was anticipating a budget cut of 23%, but instead received an increase of $75M on March 23, 2018 when the budget was passed. Dr. Bianchi noted that both Chairman Cole and Chairman Blunt, who serve on the respective appropriations committees in the U.S. House and Senate, have committed to continuing budget increases so that NIH can be competitive globally. In addition to the $75M increase for NICHD, additional funds have been appropriated for special projects. The NIH HEAL (Helping to End Addition Long-term) Initiative is an aggressive trans-agency effort to speed scientific solutions to stem the national opioid public health crisis. NIH is nearly doubling funding for research on opioid misuse/addiction and pain from approximately $600M in FY16 to $1.1B in FY18. Through an internal competitive process NICHD will receive an additional $30M of that additional allocation for a project known as ACT NOW Act II, to look at the effects of fetal and neonatal opioid exposure. Currently there are no consistent approaches to care for mothers or babies. ACT NOW is a partnership between the Neonatal Research Network and IDeA (Institutional Development Awards) States Pediatric Clinical Trials Network, which is supported by funding originally appropriated for the National Children's Study. The partnership makes it

possible to facilitate clinical trials in rural and medically underserved locations and these also happen to be states where there's a high prevalence of opioid withdrawal. ACT NOW received one year of pilot funding in September 2017 from Dr. Collins' Director's Discretionary Fund and, with this additional $30M, will continue to look at the prevalence of neonatal opioid withdrawal including the effectiveness of different treatments such as eat, sleep, and console versus medication of these babies, looking at better ways to evaluate whether they are truly withdrawing or not, and also at the effects of fetal and neonatal exposure on the developing brain.

Dr. Bianchi attended the FY19 budget hearing with Drs. Francis Collins, Anthony Fauci (NIAID), Norman Sharpless (NCI), and Nora Volkow (NIDA) where questions focused on a new trans-NIH initiative on Down syndrome, the Task Force on Research Specific to Pregnant Women and Lactating Women, and on maternal mortality. The focus of the Down syndrome initiative is not only on health and neurodevelopment, but also looking at differences in people who have Down syndrome versus typical individuals in terms of their risk for Alzheimer's disease, cancer, cardiovascular disease, immune system dysregulation, autism, and among others. Funding for this initiative will supplement, not supplant, existing NIH funding for Down syndrome research and NICHD will have a leadership role in planning the InCLUDe study. NIH funding of research on Down syndrome was approximately $27M in FY16 and this initiative will provide an additional $50M.

NICHD has not undergone a strategic planning process since 2000, though it did have a scientific visioning process in 2012. Emerging and rapidly changing challenges and opportunities along with additional funding this fiscal year and new leadership make it a great time to look at what we are doing and guide the institute's activities for the coming years. The process is already underway and NICHD leadership is analyzing a lot of impact data, especially for extramural. The major goal is to determine the future scientific focus for NICHD moving forward and align resources with those priorities. A planning committee has been meeting monthly and has been incorporating objective analyses of different areas of research. The committee is also looking at how to integrate prior strategic plans, such as those done for the DIR and DIPHR, into the overall institute strategic plan. A working group will meet for a two-day meeting, October 15-16, 2018 and will include about 80 people, half from NIH and half from the external communities. The meeting facilitator will be a company called Strategy Arts, that will be providing the graphical reporting of each presentation by creating a visual record.

The Trans-NIH Pediatric Research Consortium (N-PeRC) aims to harmonize efforts in child health research across the 27 NIH Institutes and Centers, by evaluating gaps and opportunities for collaboration and enhancing communication between NIH, advocacy groups, and Capitol Hill. NIH funding for pediatric research is currently around $4.2B across NIH and increasing. NICHD only funds about 18% of the child health research across NIH, or about $761M in FY17, representing around 55% of NICHD's total budget. The National Institute of Mental Health and the National Institute of Dental and Craniofacial Research each spend about 25% of their respective budgets on child health research. The initiative will focus on an outreach effort to encourage senior pediatric researchers to serve on review panels as well as training to grow the pediatric workforce.

NICHD continues to make progress towards inclusion of pregnant women, lactating women, children, and individuals with intellectual and physical disabilities in research. Dr. Cathy Spong

and Dr. Bianchi published a commentary on *Improving Public Health Requires Inclusion of Underrepresented Populations in Research* (*JAMA* 2018; 319:337-8). The Task Force for Research Specific to Pregnant Women and Lactating Women (PRGLAC) was established as part of the 21st Century Cures Act. PregSource is a crowdsourcing application where pregnant women can input information about their pregnancy experience. NICHD has also been actively involved in including children as well as individuals with intellectual and physical disabilities in the *All of Us* precision medicine strategic vision. Research, Condition and Disease Categorization (RCDC) is a database NIH has maintained since 2009 to categorize and report the amount of funding on more than 280 topics. Codes have not existed for pregnancy, maternal health during pregnancy, or breastfeeding but spending on these research topics have recently been tracked by the PRGLAC Task Force. Pregnant women have also been historically excluded from studies at the NIH Clinical Center. A working group has formed to examine the benefits and risks of having healthy pregnant women participate in research protocols at the Clinical Center. Good progress is being made towards greater inclusion but a change in culture is also needed. PRGLAC has made 15 recommendations to the Department of Health and Human Services and Congress stating that pregnant women and lactating women be included and integrated in the clinical research agenda; to expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology and therapeutics; and to increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women.

Dr. Bianchi noted that as Scientific Director, Dr. Stratakis is undergoing a regularly scheduled review by an external committee to evaluate his scientific vision, training and mentoring, administrative style and commitment to diversity. The review committee, chaired by Dr. Catherine Gordon, met in early April. Various groups of staff were interviewed during the meeting and a survey also went out to all DIR FTEs. A draft report is expected by early July and the committee's report will be presented at the next Advisory Council meeting in September 2018.

Finally, Dr. Bianchi announced that Dr. Cathy Spong, Deputy Director of NICHD, will be leaving the institute after more than 23 years in federal service. Dr. Spong accepted a position at the University of Texas-Southwestern in Dallas as Chief of Maternal-Fetal Medicine and Vice-Chair of the Department of Obstetrics and Gynecology.

Questions followed. A propos of NICHD's research portfolio, Dr. Bianchi said that it is roughly 55% child health, 40% reproductive health, 6.5% rehabilitation, and a small portion focused on other areas. In response to a question about how much of the additional $75M will be for targeted and how much for nondirected programs, Dr. Bianchi indicated that the specifics haven't been finalized but she expects that all programs will see a boost in paylines, with a particular focus on supporting early stage investigators. Regarding oversight of pediatric research, Dr. Bianchi said that the trans-NIH pediatric research consortium will play a big role in harmonizing efforts to avoid duplication. The consortium will meet on June 12, 2018 after which more will be communicated about the ongoing efforts. The benefit of the consortium over an office focused on pediatric research is that the consortium can identify areas of need and institutes will be able to put out their own funding opportunities.

Scientific Director's Presentation

Dr. Stratakis began his presentation by noting that there are three new members who will join the December 2018 BSC meeting: **Dr. William Dauer**, Professor of Neurology at the University of Michigan Medical School; **Dr. Petra Huppi**, Group Leader of Child Development Disorders at the University of Geneva; and **Dr. Joseph Majzoub**, Professor of Pediatrics & of Medicine at Harvard Medical School.

Dr. Stratakis reviewed the tasks of the BSC, including the main one which is to evaluate the research of NICHD DIR, our investigators, cores, and programs, and advise institute leadership on programmatic decisions and resource allocations. Dr. Stratakis stated that the goal of the intramural program is to promote high-risk, high-impact laboratory and clinical investigations, especially those that could not be readily supported in the extramural environment. The BSC reviews site visits, all our science, and advises us on the career course of our tenure-track investigators on an ongoing basis; the BSC meets twice a year, each June and December. The NICHD DIR Guidelines for Site Visit Reviews is a dynamic (i.e. continuously updated) policy document that has been in effect since 2010. Each investigator of the DIR is reviewed at least every four years utilizing ad hoc review committees chaired by members of the BSC. While the NICHD DIR uses a scoring system similar to that used in extramural study sections, the review of an intramural laboratory differs in that it covers the whole research portfolio of an investigator, not just a single project; in addition, the main evaluation of an intramural investigator is retrospective, rather than prospective, at least for tenured investigators. Site visit scores allow for prioritization between laboratories, as well as between projects within a laboratory.

The NICHD DIR's current organizational structure has been in place for three years, since October 1, 2015. Scientifically, the laboratories have self-assembled into intellectual affinity groups, with some having secondary affiliations in addition to their primary groups. Each group elects an Affinity Group Head, but this individual does not have a supervisory or administrative role. The clinical fellowship programs have been moved under the Office of the Clinical Director and the Office of the Scientific Director, providing increased support for these future physician scientists.

The Group of Senior Advisors (GSA) meets monthly to provide advice to the Office of the Scientific Director. The GSA includes all Associate Scientific Directors (ASDs) who represent their science areas and serve the needs of the PIs in their six buildings/science areas, such as managing maintenance contracts, shared equipment, and administrative staff. There are two additional ASDs, **Dr. Mary Dasso**, who serves as the ASD for Budget and Administration, and **Dr. Tracey Rouault**, the ASD for Recruitment, Retention, and Diversity. **Dr. Chris McBain** continues to serve as Deputy Scientific Director and **Dr. Forbes Porter** continues as the Clinical Director. Memberships of the GSA and affinity groups were presented. Leadership in the OSD and the Administrative Management Branch, led by **Ms. Francie Kitzmiller**, meet weekly to review all personnel, budget, and space requests.

In FY18, the DIR's budget represented 14% of NICHD's total budget. Of the approximately $186.6M the DIR received for FY18, 24% was allocated for lab consumables, 34% toward personnel, 19% toward the NIH Office of Research Services to cover buildings, maintenance, etc., and 16% was paid in support of the NIH Clinical Center. Over the last seven years, the DIR's support of the Clinical Center has increased from $24M million to over $30M this year. The

management funding to the NIH Office of Research Services has dropped as a percentage of the total budget from 21% to 19% due to the central administration's efforts to consolidate operations and keeping the costs of the overhead at reasonable costs compared to the total budget. Thanks to the BSC's reviews and recommendations to close underperforming labs or projects, the DIR has also been able to increase the proportion of the budget that goes to operating costs from about 18%, to 24% today. The DIR has allocated nearly $1.4M to support capital equipment in FY18 to date. With approximately $1.4M in renovations costs, FY18 will be the last year of a more than five-year effort to provide new or renovated space to more than 80% of staff. This process, started in 2012, cost about $18M total. Beginning in FY19, the money previously allocated for this renovation project will be added to the operating budget.

In addition to the discussed DIR allocation, DIPHR has a budget of approximately $9.5M, including $7.7M for operating costs and $1.9M in assessments.

The total size of the DIR staff has shrunk to its current level just under 900, including 301 FTEs. Staff changes were presented. Dr. Stephen Suomi retired in March 2018. Dr. Chi-Hon Lee retired from NIH in February 2018 to assume the position as the Director of the Institute of Cellular and Organismic Biology at Academia Sinica in Taiwan. Dr. Maya Lodish, Director of the Pediatric Endocrinology Inter-Institute Training Program, will be leaving to assume a position as Kaplan Chair of Pediatric Clinical Research at the University of California at San Francisco as of July 1, 2018. Dr. Stratakis announced the recruitment of a new Stadtman Investigator, Dr. Pedro Rocha, who arrived in April 2018 to establish his lab, the Unit on Genome Structure and Regulation. Dr. Rocha will present his research to the BSC at their next meeting in December 2018. NICHD participates in the NIH Lasker Program which provides physician scientists support for 5 years at NIH followed by up to 3 years at an extramural research facility or continuation in the intramural program. Applications are due by August 31, 2018 and BSC members were asked to help identify among colleagues, professional societies, and academic centers, people that might be interested in a physician scientist career at NIH, and specifically at the NICHD.

Several recent honors were highlighted including Dr. Tom Dever's election to the American Academy of Microbiology and Dr. Peter Basser's induction into the American Institute for Medical and Biological Engineering.

NICHD DIR investigators continue to be successful in competing for funding across the NIH intramural program. NICHD is the lead institute for the U-01 program, an effort to open up the NIH CRC to extramural investigators through collaborations with intramural researchers, now in its fourth cycle.

The NICHD DIR Director's Awards are in its third cycle. This competitive award was established following the recommendation from the 2013 Blue Ribbon Panel Report to foster new collaborations and support new research ideas. Applications are based on an R-21 and reviewed by a panel of NIH extramural reviewers, with successful awards receiving two years of funding. Approximately $1.4M in awards was made to investigators in FY18, and the 12 successful applications were presented.

Investigators were also successful in competing for funding from non-NICHD sources. The NIH Office of AIDS Research Strategic Funding provides funds to the highest priority, most

meritorious, research aligned with the current NIH HIV/AIDS research priorities. Three DIR investigators received funding in FY18: Drs. Anirban Banerjee, Henry Levin, and Joshua Zimmerberg.

Dr. Stratakis then reviewed the activities of the Office of Education. With the support of the BSC, Dr. Yvette Pittman was appointed the new director of the Office of Education in December 2017. The total trainee population of the DIR is approximately 269, including 178 postdocs, 53 postbaccalaureate fellows, 20 clinical fellows, and 17 graduate students, with an additional 62 summer students. The Office of Education continues to support trainees through a variety of activities, including a monthly newsletter and an Annual Fellows Retreat. The 2018 Annual Retreat was held at the Smithsonian American Indian Museum and more than 200 fellows and trainees at all levels attended.

The Office of Education also continues to support a number of initiatives to promote diversity. The NICHD Developing Talent Scholars Program, which supports postbacs and graduate students, is in its eighth year. In FY18, the Office of Education increased the number centrally-funded slots for summer students from 10 to 15 for individuals from groups traditionally underrepresented in science or from disadvantaged backgrounds, one quarter of our summer population. At the postdoc level, Dr. Alejandra Garcia in the Stopfer lab was recruited with the support of the Fellows Recruitment Incentive Award. Postbaccalaureate fellow medical and graduate school acceptances were presented.

The Office of Education is continuing initiatives aimed at public speaking, teaching, and grantsmanship. The fourth annual Three-minute Talks (TmT) Competition will be held on June 28, 2018 to promote the effective communication of science. The Office of Education has an online annual progress reporting system for postdocs which tracks mentoring activities and productivity. The reports are provided at the time of the site visit to help assess mentoring and are already beginning to produce good data.

The Office of Education has vetted grant opportunities from NIH and outside organizations, providing a list for which intramural fellows are eligible to compete. The Office also offers courses in grant writing as well as one-on-one advising. The Intramural Research Fellowships, now in its second application cycle, provides the opportunity for postdoctoral and clinical fellows to competitively write an NIH grant. Awards are $30K for one year and applications will be reviewed by the BSC.

An online exit survey for NICHD fellows will be launched as of October 2018 to obtain a comprehensive view of the fellows' training experiences and provide networking opportunities among our current trainee populations and recent alumni.

Dr. Stratakis then introduced Dr. Una Grewal, Deputy Director of DIPHR, to provide an update on the division.

Presentation on DIPHR

Dr. Grewal reviewed the mission of DIPHR, to conduct research leading to the promotion of population health and wellbeing. It includes 25 FTEs members organized into three branches: the Epidemiology Branch, the Biostatistics and Bioinformatics Branch, and the Behavioral Health

Sciences Branch. DIPHR has also been affected by the hiring restrictions, particularly the Biostatistics and Bioinformatics branch which has lost its branch chief, two tenure-track investigators, and a staff scientist in recent years that have not yet been replaced. DIPHR's FY18 operating budget was $9.5M, an 11% percent increase over the FY17 budget. This increase is the result of the expansion of the division to include the Contraceptive Development Program headed by Dr. Diana Blithe, which was previously part of NICHD's extramural program.

Dr. Stephen Gilman was awarded tenure on April 16, 2018, and subsequently appointed as the permanent chief of the Health Behavior Branch. Following his appointment, the Health Behavior Branch was renamed the Behavioral Health Sciences Branch. Dr. Pauline Mendola of the Epidemiology Branch was also awarded tenure on March 5, 2018. Dr. Zhen Chen, an investigator in the Biostatistics and Bioinformatics Branch, was awarded tenure on May 21, 2018. Dr. Enrique Schisterman, Chief of the Epidemiology Branch, received the Harold Kaminetzky Paper Prize for his coauthored publication on factors underlying the increase in maternal mortality in the United States. Dr. Katie Grantz, a tenure-track investigator in the Epidemiology Branch, was recognized with the NIH Postbac Distinguished Mentor Award. Dr. Jeremy Luk, a postdoctoral fellow in the Health Behavior Branch, was the recipient of the Junior Investigator Award and a finalist in the Enoch Gordis Award, both from the Research Society on Alcoholism.

Several scientific advances from each of the three branches were presented, showing a continuation of the division's longstanding productivity and innovative contributions to the field of population health research.

Dr. Stratakis thanked Dr. Grewal and Dr. Schisterman for their leadership during this time of transition in the DIPHR, particularly for their efforts assisting the three investigators who received tenure. A propos of whether DIPHR investigators are eligible to participate in some of the DIR activities Dr. Stratakis presented such as the DIR Director's Investigator Awards and the diversity initiatives, Dr. Stratakis said that these opportunities are now available to DIPHR investigators and the two divisions are working to increase synergies between them. Drs. Grewal and Schisterman have both been participating in the DIR's weekly administrative meeting since fall 2017. The exact relationship between the two divisions will be informed by NICHD's strategic plan but opportunities for research collaborations are already being capitalized on.

Following a short break, Dr. Stratakis introduced the next speaker, Dr. Diana Blithe. Dr. Blithe and the Contraceptive Development Program recently moved to DIPHR, from the NICHD Division of Extramural Research, where NICHD leadership thought her program was better-aligned. As she is now an intramural investigator, Dr. Blithe's research will be reviewed by the BSC, along with all other investigators in the DIR and DIPHR.

Scientific Presentations

Diana Blithe, PhD, Head, Contraceptive Development Program, DIPHR

Development of New Contraceptive Options for Men and Women

NICHD is the lead federal agency for conducting research on contraception. In 1968, the Secretary of Health Education and Welfare established the NICHD Center for Population Research. The Contraceptive Development Branch was created with the goal of developing new contraceptive methods. Promising new leads have been identified. In 2017, the Contraceptive Development Program (CDP) was established in DIPHR, with the mission to advance clinical development of novel contraceptive methods for men and women. CDP uses R&D contracts to achieve this goal: a Chemical Synthesis Facility to synthesize clinical grade pharmaceutical ingredients that are not commercially available; a Biological Testing Facility to perform preclinical testing to qualify agents for FDA-approved studies; and the Contraceptive Clinical Trials Network (CCTN) comprised of experts in clinical contraceptive development. CDP scientists coordinate and integrate the program's components to produce groundbreaking contraceptive research. The CDP investigators utilize technology transfer mechanisms to form partnerships, translating discoveries and clinical advances into products that address contraceptive needs of men and women. The CDP has a pipeline of products in clinical evaluation, including hormonal or non-hormonal options for women, and novel hormonal methods for men. Each product was developed to fill an unmet need or to provide greater safety to vulnerable populations at risk of unintended pregnancy.

Questions followed. A propos of how large of a role industry is playing in the quest for male contraceptives, Dr. Blithe said that pharmaceutical companies have not expressed a lot of interest in these male methods recently, citing concerns with liability issues and of not being able to recoup costs within the five years of patent exclusivity. Dr. Blithe's program will be scientifically reviewed by the BSC during DIPHR's next scheduled site visit in fall 2020.

Dr. Enrique Schisterman, Chief of DIPHR's Epidemiology Branch then introduced the next speaker, Dr. Edwina Yeung. Dr. Yeung is a tenure-track investigator in the Epidemiology Branch studying fetal origins of disease.

Edwina Yeung, PhD, Investigator, Epidemiology Branch, DIPHR

Developmental Origins of Health and Disease: Roles of Infertility Treatment and Parental Obesity

Dr. Yeung is a perinatal, pediatric epidemiologist investigating the Developmental Origins of Health and Disease (DOHaD) hypothesis which posits that adverse early life exposures can program cellular processes to affect long-term health. She received her PhD in Cardiovascular Disease (CVD) Epidemiology from the Bloomberg School of Public Health and became a postdoctoral fellow at NICHD in 2008. After competing in an open search, Dr. Yeung became a tenure-track investigator in 2011. Her research is focused on the roles of infertility treatment and parental obesity for developmental programming of childhood health. Accumulating research supports that CVD has early origins in perinatal factors and clearly intervening in adulthood on chronic disease risk is suboptimal when risk trajectories

could potentially be shifted much earlier in life. There is scientific evidence that infertility treatment impacts cardio-metabolic health of offspring and there are long-standing concerns over the development of children conceived with infertility treatments due to the techniques used such as in vitro culture and ovulation stimulation. As the PI of the Upstate KIDS Study, she found no evidence of major differences in either growth or development of children conceived by assisted reproductive technologies (ART) or non-ART fertility treatments compared to spontaneously conceived children through 3 years of age. Her findings are important reassuring evidence related to the use of infertility treatment techniques which millions of couples undergo worldwide. To ensure longer term health, Dr. Yeung designed the new Upstate KIDS Follow-Up Study, currently in progress, to measure cardio-metabolic risk factors through ages 8-10 years by clinical exam with biospecimen collection. Even if ART itself does not have undue influence on offspring health, factors leading to the underlying parental infertility may. To address this, she has also investigated the impact of parental obesity, a strong risk factor for infertility. Indeed, Dr. Yeung uniquely determined that maternal and paternal obesity may have independent offspring programming effects. Such novel findings, along with accumulating knowledge of epigenetics, has directed her future research to investigate paternal factors that influence offspring health.

Questions followed. The BSC commended Dr. Yeung for her fascinating research and her ability to shift from bench-to-bedside and bedside-to-bench. This type of research may be ripe for building interactions between DIPHR and basic scientists in the DIR.

Following a short five-minute break, Dr. Stratakis introduced the next speaker, Dr. Deena Zeltser. Dr. Zeltser is a staff clinician who was recruited about a year ago to serve as NICHD's Pediatric Ward Chief. In addition to their role as hospitalists, staff clinicians like Dr. Zeltser have an allocation of 20-25% of their time for professional development to pursue their own research.

Deena Zeltser, MD, Staff Clinician, Office of the Clinical Director

The ward chief position was created following the Clinical Center Red Team Report which emphasized the need to harmonize safety and science as well as to strengthen the leadership of the clinical center for proper oversight, quality, and compliance. NICHD has focused its efforts to establish systems to monitor, report, and enforce safety and quality standards, and to identify and eliminate potential gaps among clinical services. Dr. Zeltser shares the role of pediatric ward chief with two other staff clinicians, Drs. Simona Bianconi and An Dang Do who each cover the role about 10% of the year, while Dr. Zeltser covers approximately 80%. Dr. Zeltser spends the remaining 20% of her time on professional development including education, administrative responsibilities, and research and scholarship. She serves on the pharmacy and therapeutics committee, the pediatric care committee, and served as the hospitalist for the new monitored bed unit on the pediatric ward. Dr. Zeltser currently serves as an associate investigator on three protocols and will become an associate investigator on a fourth that is currently under review. She is also in the early stages of developing her own independent project under the mentorship and guidance of Dr. Stratakis to study the cardiovascular effects of hypercortisolemia before and after surgical cure from Cushing Disease (CD). This will help understand the disease processes better, and further shape the clinical management of the pre- and post-operative

periods. Tachycardia may be a sign of disorders of hypercortisolemia such as CD, although its prevalence and etiology remain unknown. She observed that patients remain tachycardic at least one week after surgical cure from CD, despite low or undetectable cortisol levels. Some patients even had worsening tachycardia despite their cure from CD. Other common etiologies of tachycardia in the immediate post-operative days include pain, hypovolemia, anemia, and/or infection. Seven to ten days after surgery, however, these issues are typically resolved. This clinical observation of persistent tachycardia in newly eucortisolemic patients paves the way to explore other potential etiologies of tachycardia in patients with CD. In addition to cortisol-mediated catecholamine-release causing tachycardia in CD, there is a direct biochemical effect of cortisol on the purkinje fibers of the heart, thereby causing tachycardia as well. The latter effect may take longer to resolve, thereby causing lasting tachycardia. By the same theory, patients with adrenal sources of their hypercortisolemia should also be tachycardic before and after surgical cure.

Questions followed. There was discussion on the use of clinical data generated at the NIH CRC, such as the data that Dr. Zeltser is working with. In response to a question about how she will balance all her activities, Dr. Zeltser said that her hospitalist role is her main function and, while she wants to be a physician-scientist, her focus will remain on clinical service and care. As senior faculty, Dr. Forbes Porter and Dr. Stratakis will be providing guidance and mentorship of how to balance her time.

Dr. Stratakis then introduced the final speaker of the open session, Dr. Brant Weinstein. Dr. Weinstein, a zebrafish physiologist, is an Associate Scientific Director who has been instrumental in running NICHD's aquatics facility. Dr. Weinstein has requested some resources within the aquatics facility to develop a new project looking at cavefish, which is why he was asked to present to the BSC.

Brant Weinstein, PhD, Head, Section on Vertebrate Organogenesis

Astyanax mexicanus: A model for studying developmental epigenetics

The cavefish *Astyanax mexicanus* is a superb complementary fish model organism with a series of uniquely evolved adaptations including loss of eyes and pigment, dramatically altered metabolism, altered vascular function, and altered sleep regulation and behavior. Despite their very dramatic phenotypic differences, Pachon cave and surface morphs of *Astyanax mexicanus* are only separated by about a million years of evolution. Recent work from the Weinstein laboratory suggests that altered DNA methylation and resulting coordinated changes in gene expression have helped to drive at least some of this rapid evolutionary change. Thus, this model provides a powerful platform for studying the potential role of epigenetics in eye development, metabolism, the vasculature, etc. Epigenetic changes have already been implicated in visual, metabolic, blood, vascular, and other human diseases, so the cavefish model may also provide useful insights eventually applicable to the clinic. The goal of the Weinstein lab is to maintain a small colony of *Astyanax mexicanus* at the NICHD as a complementary model to the zebrafish, their main aquatic model, and use them to help examine the role of epigenetics in regulation of vascular function, metabolism, and eye development. To facilitate their studies and the growing wider use of this model, they will also use their expertise to establish several

critical new foundational experimental and genetic tools including transgenic reporter lines, molecular markers, and genomic resources.

Questions followed. A propos of the resources necessary for this work, Dr. Weinstein has gotten a quote from NICHD's Research Animal Management Branch, that it will cost approximately $30K per year to keep the number of fish he is requesting. In response to another question about housing the cavefish in a facility with light, Dr. Weinstein indicated that his colleague in building 6, Dr. Harold Burgess, studies non-eye visual detection and that he would be interested in looking at whether cavefish are actually exhibiting behaviors suggesting that they are sensing light. Until now, Dr. Weinstein has been working with a collaborator, Dr. Bill Jeffrey, who has been housing the fish in his lab at the University of Maryland. Dr. Stratakis noted that this project was reviewed well during Dr. Weinstein's last site visit but with the scaling up of resources, he wanted the BSC to have the opportunity to hear from Dr. Weinstein.

With that, the open session concluded.