

**ROBERT'S PROGRAM ON SUDDEN
UNEXPECTED DEATH IN
PEDIATRICS**

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Robert's Program 2019 Annual Newsletter

Each year, we share a summary of our ongoing efforts with our community, made up of the families we are so privileged to try to help, and the families and friends whose generosity makes our efforts possible. This is our latest report, covering 2018.

Goodbyes and Hellos

Among the most significant developments of last year, Dr. Hannah C. Kinney retired and became an emeritus professor. Quite simply, no one has ever accomplished so much in the area of basic SUDP research. She left an enormous footprint and her absence is strongly felt. Our program was also affected by the retirement of Dr. Henry Nields, the Massachusetts Chief Medical Examiner who was instrumental in getting our program started. Both of these fine physicians were extraordinarily important to our efforts, and to the field. They are irreplaceable.

Dr. Rick Goldstein remains the director of Robert's Program, and Dr. Ingrid Holm began as the associate director. Dr. Robin Haynes assumed leadership of the Kinney Laboratory, now the Haynes Laboratory, as of 1 March 2018. Dr. Sanda Alexandrescu has assumed neuropathology responsibilities for Robert's Program as Dr. Kinney's successor. Dr. Alexandrescu's work has previously focused on brain tumors in children but she is extremely enthusiastic to be involved. We welcomed a new program coordinator, Christine Keywan, who is a genetic counselor and a fantastic addition. Kalen Fletcher left the program to practice social work at Beth Israel Deaconess Medical Center.

Our work with families

Robert's Program continues to enroll Massachusetts families in our program of comprehensive clinical care for sudden unexpected death in pediatrics (SUDP), including SIDS, SUDC and SUDEP cases. Our bereavement support program has become more formalized, and our efforts have been expanded with more regular offerings. The new Chief Medical Examiner for Massachusetts, Dr. Mindy Hull, has not expressed the same enthusiasm for our program as her predecessor, but word seems to be getting out to families who may benefit from our services. Because our collaboration has changed locally, we are now offering our assistance to families

outside of Massachusetts at no cost to them so long as our resources allow, and enrollment in that part of the program continues to increase as well.

New Publications

Brownstein CA, Goldstein RD, Thompson CH, Haynes RL, Giles E, Sheidley B, Bainbridge M, Haas EA, Mena OJ, Lucas J, Schaber B, Holm IA, George AL, Kinney HC, Poduri AH. SCN1A Variants Associated with Sudden Infant Death Syndrome, Epilepsia, 2018.

Pearl PP, Poduri A, Prabhu S, Harini C, Goldstein R, Atkinson RM, Armstrong D, Kinney H. White Matter Spongiosis with Vigabatrin Therapy for Infantile Spasms, Epilepsia, 2018.

Robert's Program researchers had a major publication this year announcing an epilepsy gene found in infants dying from SIDS. "*SCN1A Variants Associated with Sudden Infant Death Syndrome*", published in the journal *Epilepsia*, presented our discovery of an epilepsy gene in two infants who died of SIDS with hippocampal abnormalities. The gene had previously been described in a severe epilepsy syndrome called Dravet's Syndrome. Better understanding the basis for the epilepsy-like changes in the brain anatomy of some infants dying from SIDS is an important focus of our work.

Robert's Program researchers were also involved in "*White matter spongiosis with vigabatrin therapy for infantile spasms*", also in *Epilepsia*. This paper described changes in the brain of a child with epilepsy who died unexpectedly during sleep, and presents evidence that those changes may have been due to an anti-epileptic medication he had received for treatment.

Morris S, Fletcher K, Goldstein RD. The grief of parents after the death of a young child. J Clin Psychol Med Settings. 2018.

Goldstein RD, Lederman RI, Lichtenthal WG, Morris SE, Human M, Elliott AJ, Tobacco D, Angal J, Odendaal H, Kinney HC, Prigerson HG; PASS Network. The grief of mothers after the sudden, unexpected death of their infants, Pediatrics. 2018.

Goldstein RD, Petty CR, Morris SE, Human M, Odendaal H, Elliott A, Tobacco D, Angal J, Brink L, Kinney HC, Prigerson HG; PASS Network. Pre-loss personal factors and prolonged grief disorder in bereaved mothers. Psychol Med. 2018.

We had 3 articles in 2018 that made significant contributions to grief research. Drs. Goldstein and Morris, with Kalen Fletcher, published a review in the *Journal of Clinical and Psychological Medicine*, entitled "The grief of parents after the death of a young child". The article summarizes research on grief that has focused on young families after the death of a child. The review highlights the severe challenges of young parents after the death of a child and suggests that it may be worthy of its own attention as a specific subset of grief responses.

The Pediatrics paper describes the characteristics and severity of grief in mothers after their infants die from SIDS. The prevalence of prolonged grief disorder is very high and persistent. Role confusion and anger were shown to be prevalent features of their grief. The severity of symptoms was the same whether the mothers were rich or poor, and wherever they lived.

Drs. Goldstein and Morris also published, “Pre-loss Personal Factors and Prolonged Grief Disorder in Bereaved Mothers”, in the journal Psychological Medicine. This research helps understand characteristics of mothers existing before the death of their infants that influence the severity of their grief-related symptoms after their child dies. A history of depression, alcohol use, the presence of other children in the home, among other factors, were all found to be associated with different trajectories of grief. This research has the potential to help prioritize bereavement services to parents who most need them.

Robert’s Program was well represented in a new international textbook on SIDS. We were authors of 4 chapters in the book ” SIDS, Sudden Infant and Early Childhood Death: The Past, the Present and the Future” (JR Duncan and RW Byard (editors), University of Adelaide Press, Adelaide, Australia. 2018).

The chapters were:

Kinney HC, Haynes RL, Armstrong DD, Goldstein RD. Abnormalities of hippocampus in sudden and unexpected death in early life.

Brownstein CA, Poduri A, Goldstein RD, and Holm IA. The Genetics of Sudden Infant Death Syndrome.

Haynes, RL, Biomarkers of Sudden Infant Death Syndrome.

Goldstein RD. Parental Grief.

Ongoing Research and Grants

We are in the process of significantly increasing the number of SUDP cases with whole exome sequences for our program. This sequencing has been underwritten by donations from families and involves DNA from research repositories and families enrolled in Robert’s Program. Greater numbers should hopefully lead to high yield genetic studies in the next year or so. We additionally received R21 funding from the NICHD for research in “Genetics of sudden unexpected death in pediatrics” (Goldstein, Poduri, Holm) and will use the genetics data of Robert’s Program along with our phenotype data to identify new genes and/or mechanisms that explain deaths in SUDP.

We have received a grant from the Cooper Trewin Brighter Days charity (Australia) to support the further development of our comprehensive gene panel for SUDP, in collaboration with the Broad Institute at MIT and Harvard. The project’s goal is to develop an affordable gene panel to be made available as a clinical screening tool, including the reliable, precise capture of the 254 genes we have identified to be of interest in the evaluation of any case of sudden unexpected death in pediatrics. In this collaboration, we are also developing the capacity to assess structural variants in these genes, i.e. gene deletions and duplications, from exome data. Once developed, this useful tool will be made widely available to medical examiners, other physicians, and families.

Research in Dr. Hayne's R01, "The Hippocampus and Brainstem in the Sudden Infant Death Syndrome", an effort to link the hippocampal findings associated with SIDS and SUDC with Dr. Kinney's earlier work in the brainstem, is ongoing. This includes an analysis to compare exome sequences derived from brain tissue with other body tissues in SIDS patients in whom abnormalities were found in the dentate gyrus of their hippocampus, to assess whether there is localized genetic variation. Other continuing research includes the NICHD funded "Ontogeny of Brainstem Arousal Networks in Human Consciousness" (Kinney, Goldstein), which studies the relationship between neural networks and cognition in the fetus and early life using connectomics. Two research programs in their final phases are "The Ventral Medulla and The Sudden Infant Death Syndrome", Dr. Kinney's productive program project with the NICHD that has explored the role of medullary 5-HT abnormalities in the pathogenesis of sudden infant death in animal models; and a grant from Citizens United to Cure Epilepsy, "The genetics of sudden unexpected death in pediatrics and hippocampal pathology- a novel entity linking SIDS and SUDC to Sudden Unexpected Death in Epilepsy Patients" (Poduri, Goldstein), research that led to the discovery of the SCN1A gene mentioned above.

Dr. Robin Haynes was awarded a grant from the American SIDS Institute focusing on the potential use of blood samples from newborn screening to assess risk for SIDS, examining serotonin levels in dried blood spots taken at birth.

Conferences and Presentations

We are extremely pleased to announce **the C.J./Kinney Endowed Lecture on Sudden Unexpected Death in Pediatrics**. This lectureship has been made possible by a generous gift from the C.J. Foundation for SIDS and its founders, Susan and Joel Hollander. The Hollanders have been influential supporters of SIDS research and their gift will make possible an annual lecture at Harvard devoted to the newest developments in the field. In addition to recognizing Hannah Kinney's unique contributions to the science of sudden unexpected death in pediatrics, the lectureship will allow us to bring a major contributor in the field to come lecture and share their work with our program each year. The event will include a medical grand rounds lecture followed by a parent luncheon. We are extending a big invitation to families associated with our program to join us and then stay for a luncheon. The luncheon is intended specifically for parents to interact, and to discuss the state of research in our field with our speaker and members of the Program. ***May 1, 2019 is our inaugural Rounds and its title is: "Sudden Infant Death Syndrome, Breathing Recovery, and Serotonin"***. *Please save the date!*

The inaugural speaker will be Dr. Susan Dymecki, Professor of Genetics and the Director of the Biological and Biomedical Sciences PhD Program at Harvard Medical School. She has made major contributions toward our understanding of the serotonergic system, and has been an important and trusted collaborator with Hannah Kinney. Dr. Dymecki's research uses genetic, embryological, and molecular biological methods to explore how embryonic cells differentiate into different types of neurons, including serotonergic neurons and their involvement in such disparate functions as sleep, arousal, homeostasis, pain, and depression. Her lab has generated a variety of recombinase-based transgenic tools to define progenitor-progeny cell relationships, distinguish cell lineages based on molecular identity, and perturb these lineages in various ways to reveal cell function in the living mouse. Her insights into the complexities of the serotonergic

system have important bearing on the future of SIDS research, and build on Hannah's key discoveries. Please make an effort to attend.

In November, we hosted **the 3rd International Congress on Sudden Death in Infants and Children at the Radcliffe Institute**. This meeting included leaders in SIDS and SUDC from around the world. In attendance were representatives of the Centers for Disease Control and Prevention (US), National Association of Medical Examiners (US, Canada), American Academy of Pediatrics (US), the International Society for the Study and Prevention of Perinatal and Infant Death (International), leading basic science and epidemiological researchers from around the world (US, UK, Norway, Germany, New Zealand), and included pediatricians, pediatric pathologists, forensic pathologists, family physicians, epidemiologists, statisticians, researchers, and parent representatives.

After two days of debate, the following conclusions were unanimously reached.

- Four diagnostic categories (ICD-11 categories of *MH11*, *MH12*, *MH14*, *PB00-PBoZ*) were presented for WHO ICD classification and explicit definitions and guidance were provided for death certifiers.
- The definition for SIDS was reframed as *Unexplained Sudden Death in Infancy or Sudden Infant Death Syndrome*, allowing for emphasis about the lack of explanation following a rigorous investigation.
- Explicit guidance was provided for the use of alternative categories (“*undetermined*” or “*accidental suffocation*”), so that death certifiers can be clear about how the categories are defined and what their judgments at death certification imply.
- A diagnostic category of “*Unexplained sudden death in children and adults*” was developed and recommended, to assure the international surveillance of SUDC mortality.

It was a great success and its conclusions will be shared with the World Health Organization to advise on international classification of SUDP deaths in the ICD-11. A summary of the Congress is currently being prepared for publication. The recommendations from the Congress will be disseminated among international forensic pathology and pediatric organizations.

Robert's Program faculty have spoken widely about our work. Dr. Ingrid Holm presented “The genetics of sudden unexpected death in pediatrics” at the 2018 Pediatric Academic Societies meeting. Robert's Program had six presentations at the meeting of the 2018 International Society for the Study and Prevention of Infant Death: “The genetics of sudden unexpected death in pediatrics” (Holm); “Combined prenatal alcohol and smoking increases the risk for SIDS: Report of the Safe Passage Study” (Haynes); “5-HT1A binding deficiencies in the rostral serotonergic raphe system of the sudden infant death syndrome” (McConville); “The role of sodium channels in sudden unexpected death in pediatrics” (Rochtus); “Managing families with recurrent SIDS: international collaboration, new diagnoses and ethical challenges” (Goldstein); Pathology Symposium Panel (Goldstein). In addition, Michael McConville was the recipient of the first annual Hannah Kinney Travel Award for the Advancement of SIDS Research and Dr. Goldstein was given a travel award to the ISPID meeting. Dr. Haynes lectured in Cape Town South Africa as part of the Feedback to Health Care Workers and the Community Symposia for the Safe Passage Study, presenting data from the study showing epidemiological evidence of an increased

risk of SIDS as a result of prenatal drinking and smoking, and pathological evidence of abnormalities in SIDS infants in the nicotinic acetylcholine neurotransmitter system. Drs. Holm and Goldstein both made presentations at the American Association of SIDS Prevention Physicians meeting. Dr. Goldstein was keynote speaker at the 2018 California SIDS Conference, a speaker at the 2018 annual meeting of the National Association of Medical Examiners and also delivered a plenary on Children without a Diagnosis at the 4th Global Gathering on Paediatric Palliative Care, in Rome, Italy.

Advocacy Efforts

On our behalf, parent alumnae of our program have begun a process of legislative advocacy to potentially assure greater collaboration with the Massachusetts Office of the Chief Medical Examiner. An awareness program with the Massachusetts Funeral Directors Association is in development, in order to make them aware that our services and supports are available to greater numbers of families. We encouraged families to submit comments to the proposed NICHD strategic plan, and hope we will see some impact from all the many efforts.

A Message from Rick Goldstein

I feel like we have come a long way since the uncertain ideas that Hannah and I shared. While we are not satisfied with our accomplishments, it is fair to say that the idea of a program that provides deeper explanations for SUDP, supports families on their terms, and uses these interactions to motivate research is succeeding. We are gaining new insights in every area of the program, and have grown more confident in what we do. We now have a “standard approach” for our investigations, and a cohesive group has developed in Robert’s Program with a unique understanding of the problem and great, but founded, enthusiasm for new ideas. We are making important and steady contributions to medical research, and have an influence on the way the problem of SUDP, and affected families, are seen. We are offering our diagnostic services nationally and internationally. We are getting better at this.

Still, we wish there was more sympathy for what we are trying to respond to and accomplish. We continue to be disappointed by Massachusetts medical examiners, who do not see the problem as the crisis it genuinely is and fail to engage in order to help affected families. This may be balanced by the helpful and energetic collaborations that are developing with forensic pathologists elsewhere, but it is a disappointment nonetheless. We continue to seek grant funding, always difficult, and are extremely reliant on the generosity of the families we serve, which can seem unfair. For us, the stakes seem too high to do anything less than push on as hard as we can.

I feel grateful to our donors, big and small, every time I say to a family that, because of others who have been in their shoes, we are in a position to do what we need to do. It is a privilege to tell them that they don’t have to worry about what it will cost because of your generosity. You are all in the room with me at that time. The comfort that comes from serious attention and leaving no stone unturned is a comfort your generosity helps provide. I think that alone is one of the most extraordinary things I do.

SUDP is a complicated and tragic problem. We are trying to address it using new approaches and ideas. We are routinely amazed by the ways that families bear up under their difficulties, and are

privileged to see the best of the human spirit all the time. It brings out the best in us, and we can only hope that we are making meaningful contributions to your lives and the value of the lives we have lost. On behalf of Robert's Program, we sincerely thank you.

Richard D. Eldstein, MD

