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SEQUENCE
Decoding news and trends for the medical genetics community

By Deborah Levenson

## RESEARCH UPDATE

# DAVID W. SMITH WORKSHOP CELEBRATES 30 YEARS OF DISCOVERY

*Exchange of ideas and resulting advances are noted dysmorphologist's legacy*

Thirty years ago, a group of about 100 clinicians and basic scientists who were interested in birth defects gathered at the University of California, San Diego (UCSD) for informal, collegial discourse aimed at better understanding how human malformations occur and the underlying mechanisms of morphogenesis. The gathering, the first David W. Smith Workshop, marked the beginning an annual tradition of discussion, debate, and diversion among dysmorphologists, geneticists, pediatricians, and researchers who study birth defects.

The workshop—held this year in Union, Washington, August 27–September 1—has gained a reputation as a productive and fun venue for sharing and pondering new discoveries and emerging theories. Traditionally, only about 125 individuals—selected based on review of their abstracts by a scientific program committee—attend the summer workshop. Each participant makes a short presentation of hypothesis-driven findings related to 1 of 3 to 5 themes. The intense discussion that follows has spurred collaborations, new research, and discoveries that have improved treatment for children with birth defects.

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The David W. Smith Workshop has been instrumental in furthering advances in the fields of dysmorphology and genetics and mentoring the next generation of researchers.

### The Legacy of David W. Smith

The meeting honors the memory of David W. Smith, MD, widely known as the father of dysmorphology, a discipline that embraces study of genetics, environmental factors, and embryology in diagnosis of birth defects and developmental abnormalities. Dr. Smith died in 1981 at age 55, following a career marked by major accomplishments and the admiration of his colleagues and trainees.

Trained as an endocrinologist, Dr. Smith ran a pediatric endocrinology program at Johns Hopkins University in Baltimore, Maryland, very early in his career. There he realized that many of the growth problems that affected his patients were due to birth defects rather than endocrinology problems, according to Kenneth Lyons Jones, MD, Chief of the Division of Dysmorphology–Teratology in the Department of Pediatrics at UCSD. Dr. Jones, one of Dr. Smith's fellows, organized the first David W. Smith Workshop.

After a sabbatical spent studying embryology in Europe, Dr. Smith started studying abnormalities of structure at the University of Washington in Seattle and began the early work that led to establishment of the field of dysmorphology. This new field grew out of the study of birth defects that, prior to the mid-1960s, was known as teratology—literally the study of monsters—a term that still exists but is used less frequently today, Dr. Jones says. In 1966, a paper written by Dr. Smith and published by the *Journal of Pediatrics* was the first to discuss dysmorphology [1966]. The emerging field addressed birth defects from any cause—including environmental and genetic causes—and sought to understand the mechanisms that give rise to both normal and abnormal human development, explains Dr. Jones.

Dr. Smith both coined the term "dysmorphology" and refined the terms used for children's anomalies such that "more subtlety entered discussion of birth defects," says geneticist Roger E. Stevenson, MD, Director of the Greenwood Genetic Center in Greenwood, South Carolina. Dr. Smith went beyond discussing syndromes as groups of symptoms to pinpointing the causes of the syndromes. He began describing malformations, disruptions of normally formed organs, and deformations of existing body parts. He also referred to dysplasias, tissue that does not form properly, and disruptions, which are body parts that form correctly but disappear due to structural alterations, explains Dr. Stevenson.

Dr. Smith popularized the idea that every pediatrician should be a dysmorphologist, Dr. Stevenson adds. Dr. Smith maintained that children's physicians must

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understand something about the morphology of structures they see. "He didn't want to relegate dysmorphology to some ivory tower," Dr. Stevenson recalls.

A compendium on short stature, of which Dr. Smith was an author, appeared in the *Journal of Pediatrics* [1965]. It was the forerunner to his many well-known books, including *Recognizable Patterns of Human Malformation, Recognizable Patterns of Human Deformation*, *Growth and Its Disorders*, *Introduction to Clinical Pediatrics*, and *Biologic Ages of Man*. Another book, *The Child with Down's Syndrome (Mongolism): Causes, Characteristics and Acceptance for Persons Concerned with His Education and Care*, was written specifically for parents. This book was also innovative, recalls Dr. Jones, because "there wasn't much written for parents back then."

Dr. Smith was the first to recognize trisomy 13 and the second researcher to report on trisomy 18. He was also involved in discovery of a number of conditions associated with birth defects, lending his name to several, including Aase-Smith, Smith-Lemli-Opitz, and Marshall-Smith syndromes. "Smith typically put other people first, so many other conditions he first described do not bear his name," notes John Graham, MD, Director of Clinical Genetics and Dysmorphology at Cedars–Sinai Medical Center in Los Angeles, California, and another of Dr. Smith's fellows. These conditions include Klinefelter syndrome and Turner syndrome. Several other syndromes were discovered using Dr. Smith's methodology, Dr. Graham adds.

Together, Drs. Smith and Jones were the first North Americans to describe fetal alcohol syndrome in 1973, after identifying a pattern craniofacial, limb, and cardiovascular defects associated with prenatal onset growth deficiency and developmental delay in 8 unrelated children of 3 ethnic groups, all born to mothers who were alcoholics.

David W. Smith, MD

## The Workshop's Beginning

The Smith Workshop emerged during a 1979 teratology meeting and was inspired by frustration over the lack of attention to malformation, Dr. Graham recalls. At a gathering in an airport bar, Dr. Smith lamented the dearth of such discussion and invited both Dr. Graham and Dr. Jones to envision their ideal meeting. He handed a notepad to Dr. Jones, Dr. Graham notes.

"What we came up with was a workshop in which all attendees submit abstracts and participate in discussion. There would be only 100 participants who would meet for about 4 days to think about morphogenesis and malformation," Dr. Graham recalls. "Dave asked Ken to organize the first meeting, and I agreed to do it the following year. Dave had already passed away by then."

The first workshop and the 30 subsequent ones have been opportunities for clinicians, researchers, and trainees "to bring the most important thing they are doing related to understanding abnormalities of structure to others in the field," says Dr. Jones. "We comment and learn from each other in an informal way." Limiting participation to 125–130 people allows for such interaction. "This gathering isn't meant to be about passive listening," he adds, explaining that the term "workshop" underscores the central importance of all attendees' contributions.

The chairs of the 2010 meeting emphasize this point. The meeting is unique because all participants present their work and debate, says Sonja Rasmussen, MD, Senior Scientist at the Centers for Disease Control and Prevention, and Michael Bamshad, MD, Professor of Pediatrics at the University of Washington. "At other meetings, you're often there either to learn or just to present," Dr. Rasmussen explains. "The Smith meeting is small so people can feel comfortable discussing controversial topics that non-Smith attendees aren't interested in."

The meeting has developed a reputation for mentoring fellows and younger people in the field. "The meeting in general is good for fellows because of its interactivity. New fellows eat with authors of key books on genetic disorders," Dr. Rasmussen explains. Praising the way the meeting promotes mentorship, she recalls her first workshop, at which she sat between the authors of 2 texts that she had used in her fellowships. "I still turn to them for guidance," Dr. Rasmussen notes. "This sort of thing honors the legacy of David Smith. It's an example of how we carry on his work."

**The Smith meeting is small so people can feel comfortable discussing controversial topics that non-Smith attendees aren't interested in.—*Sonja Rasmussen, MD***

## The 2010 Lineup

Each year, the workshop's organizers identify "hot topics" as themes for the meeting. For 2010, the themes were race, ethnicity, and birth defects; disorders of sensory perception; novel strategies to understand the causes and mechanisms of birth defects; and adults with dysmorphic syndromes.

Speaking with "The AJMG Sequence" prior to the workshop, Dr. Rasmussen was excitedly anticipating presentations and discussion of novel strategies for understanding the causes of birth defects. Among them is exome sequencing, described by Dr. Bamshad and colleagues [Ng et al., 2010]. By looking at every coding gene in the human genome in a single experiment, the researchers were able to identify *DHODH* gene mutations that cause Miller syndrome. They used only a very small number of unrelated cases to uncover the genetic culprit for the disorder, which causes malformations in the mouth, eyelid, ears, and feet.

Since Dr. Bamshad presented this research at last year's Smith Workshop, the strategy has become more popular and has been used to better understand other syndromes, including Fowler syndrome. McGill University researchers recently used exome sequencing in just 2 patients to identify 3 types of the disorder [Lalonde et al., 2010].

**[Dr. Smith] didn't want to relegate dysmorphology to some ivory tower.**
***—Roger E. Stevenson, MD***

Adults with dysmorphic syndromes was chosen as a theme because so much about their presentation and natural history has been learned in the past few years, explains Dr. Bamshad. Included among these disorders are Cornelia de Lange syndrome—marked by poor muscle tone, low levels of sex hormones, constant feelings of hunger, and short stature—and Williams syndrome—with symptoms including developmental delays, speech problems, attention deficit disorder, feeding problems, and unusual facial appearance.

Last year's lively discussion of gastroschisis, an abdominal wall defect that is increasing in prevalence, was exactly the sort of exchange the meeting is meant to promote, says Dr. Bamshad. Debating hypotheses of how the condition develops is something that would not necessarily interest other medical specialists involved in the research and care of birth defects.

**[Dr. Smith's] life's work was to better understand the causes of normal and abnormal development, and the meeting is part of his legacy.**
***—Kenneth Lyons Jones, MD***

## Change and Continuity

Advances in the fields of dysmorphology and genetics since the first workshop in 1980 have driven changes since then, say Drs. Jones and Stevenson. While early meetings were exclusively focused on structural changes, more recent workshops—especially those in the past 10 years—have focused more on the molecular genetics at the root of many birth defects, notes Dr. Stevenson. "Now, some presentations make no mention of structural changes," he points out.

"If Dave Smith were alive today, [things] would be moving in the same [direction]," Dr. Jones adds. He takes stock of the workshop's many achievements. One is the mentorship and training of a large number of young doctors who see children with birth defects. "This is a huge accomplishment. Birth defects are not going away, so we need to train people," he explains.

Dr. Jones also points to many important observations that were first publicly discussed at the workshop. He recalls first learning the specifics of research pinpointing the specific genetic causes of both Prader-Willi syndrome—which involves developmental disabilities, slow growth, and abnormal skeletal and facial features—and Cornelia de Lange syndromes at the Smith Workshop.

These accomplishments were made possible by what has remained the same at the workshop: the meeting's small size and informal—and often lighthearted—atmosphere. Dr. Graham, who describes Dr. Smith as "the Pied Piper of dysmorphology," recalls one of Dr. Smith's rules for the first workshop: Business must be transacted in song format. Although Dr. Smith is no longer there, "we still work hard and we still play hard," Dr. Stevenson says.

For more experienced researchers, the Smith Workshop's informality and interaction has given rise to many productive research partnerships, Dr. Stevenson points out. Spurring these collaborations is discussion between "basic science people who never see patients" and clinicians, which allows researchers to explain their work and clinicians to offer ideas about topics that need study, Dr. Rasmussen adds, saying, "This interaction is the reason this meeting is one I never miss."

These connections and the resulting gains in knowledge are "what this meeting is all about," adds Dr. Jones. "[Dr. Smith's] life's work was to better understand the causes of normal and abnormal development, and the meeting is part of his legacy."

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