EDITORIAL COMMENT

THE CLINICAL DELINEATION OF MALFORMATION SYNDROMES: HISTORICAL PROSPECTIVE AND FUTURE DIRECTION

Initiating a current dialogue on the delineation of malformation syndromes represents a timely and relevant discourse because of three recent landmarks. The first of these events -and likely the most important- is the 2007 Commentary by Raoul Hennekam[1]. In this piece, Hennekam argues that once the "molecular era started", the delineation of a syndrome became more complicated. He underscored the fact that mutations of a single gene are now known to cause "various combinations of manifestations, which (before) we had delineated as the distinct" entities and this created new challenges. The problem became whether these various syndromes "should be kept separate or merged" into a single disorder. We will return to this dilemma below.

The second event was the publication of a series of papers entitled "The Elements of Morphology" in 2009 in the *American Journal of Medical Genetics*[2]. The six articles accompanied by an introduction were the end product of five years of work of an International Working Group of 34 clinical geneticists and dysmorphologists from the United States, Canada, Europe and Australia. The authors of these articles proposed standardized consensus definitions and terminology for more than 400 phenotypic variations of the craniofacies and limbs. With the establishment of this working group, an infrastructure was established that could allow for further work on the nomenclature and definition of terms in syndromology. More on this below.

Lastly, 2009 marked the 40th anniversary of the publication of First Conference on the "Clinical Delineation of Birth Defects", a meeting hosted by Victor McKusick at John Hopkins University in Baltimore the previous spring. Over four years, 1968 to 1971, the esteemed Professor of Human and Medical Genetics (and certainly the founding father of the field) orchestrated these annual conferences attended by many of the now recognized pioneers in medical genetics. The meetings included invited lectures, scientific talks and patient presentations; the solicited papers and patient reports were published in a series of "blue books" by the National Foundation of March of Dimes as the *Birth Defects Original Article Series* (these blue hard-bound books are treasures and are still on the shelves of many of us in the field). These works are now considered to have galvanized the study of human congenital malformations; they established the principles of human genetics as applied to the

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study of birth defects and created a forum for documenting the **first step** in the delineation of malformation syndromes, the observation and documentation of a provisionally unique pattern of malformation. At the first conference, several now well established syndromic entities, such as the Opitz BBB/G syndrome, the Bixler syndrome and the C syndrome, were originally reported. Other conditions, including Smith-Lemli-Opitz syndrome, the Pierre Robin sequence (then "syndrome") and the Meckel-Gruber syndrome, were more clearly delineated.

At that First Conference on the Delineation of Birth Defects, two monumental talks occurred: 1) An evening lecture by Dr. McKusick entitled "On Lumpers and Splitters or Nosology of Genetic Disease" (a paper that should be read by all students and authorities alike on a periodic basis[3]) and 2) a seminal lecture by Dr. John Opitz, "The Study of Malformation Syndromes in Man"[4]. Both presentations introduced the basic tenets of syndrome delineation now familiar to all of us in the fields of medical and clinical genetics.

The objective of this Comentario Editorial is to celebrate and draw attention to these events (accomplished in the above paragraphs), to provide a historical background for the concepts of **syndrome and syndrome delineation**, and to suggest the need for rethinking the definition of the key terms and nosologic groupings in birth defects.

Nomenclature and Definition of the Term Syndrome: recommended definitions for the commonly used terms of morphological defects (e.g. malformation, deformation and syndrome) have been proposed by three different international working groups since 1975:
1) In February 1975, a group of esteemed clinical geneticists including David W. Smith, John M. Opitz, Robert J. Gorlin and M. Michael Cohen, Jr., met at the National Institutes of Health to "discuss suggestions for classification, nomenclature and naming malformations." At that meeting the term "anomalad" was proposed for what we now call a sequence (the term was abandoned and superseded by sequence at the next meeting). At the 1975 conference, malformation syndrome was defined as "a recognized pattern of malformation presumably having the same etiology and currently not interpreted as a consequence of a single localized error in morphogenesis, e.g. Down syndrome."[5]
2) The second meeting was chaired by Dr. Jurgen Spranger and also included Drs. Optiz and Smith and was published in the *Journal of Pediatrics* in 1982[6]. As mentioned, the term "anomalad" was replaced by sequence (now in current use); syndrome was defined as a "pattern of multiple anomalies thought to be **pathogenetically** related and not known to represent a single sequence or polytopic field defect" (my bold). The term polytopic field defect was also defined in their article.
3) The third International Working Group convened in Berlin in 1987[7]. The consensus of the participants at that meeting indicated that the term syndrome should relate to its original meeting as written by Gruneberg in his book of 1974[8]. Here syndrome denoted a "causally defined entity" and was specifically defined

at the Berlin meeting as a "recognizable pattern of anomalies which are known or thought to be **causally** related." Note that the term causally replaced the term pathogenetically that had been proposed at the second meeting. Spranger, who had chaired the second group, authored the specific section "What is a Syndrome" (a title similar to what Hennekam used in his 2007 Commentary) and closed his piece of the paper by indicating that the term syndrome should not be applied to "polytopic field defects and sequences", making the distinction between these different classes of malformation patterns. The authors pointed out that the term syndrome in common medical usage has not only a causal, but also a pathogenetic, connotation.

Notably, no working group has met over the last two decades while there has been considerable coverage in the literature on the use of the terms sequence and association, both discussed at the Berlin meeting. The revised consensus term for syndrome proposed at the Berlin meeting - now ideally used by geneticists throughout the world – is a more specific designation than the more nonspecific usage in conventional medicine.

In prior publications, John Opitz[4,9] had outlined the stages of syndrome delineation and definition (**delineation** referring to the study of phenotype and natural history, while **definition** to the elucidation of cause):
1) The first stage is the initial observation of the multiple anomalies in the originally described patient (or patients). Here the likelihood that the observation is a true syndrome (referred to by Opitz as "causal or true syndrome") and a discrete, discontinuous pattern increases the more "anomalies that the patient has" and the "more rare these anomalies are in the normal population".
2) The second stage of a syndrome delineation and definition called formal genesis (a term that has not reached common usage in the genetics community) involves the identification of a similar set of anomalies in an increasing number of patients; here the clinical boundaries and clinical criteria of the emerging syndrome, the **second step of syndrome delineation** (as suggested by myself in a recent editorial[10]) are set forth.
3) The third stage -causal genesis- is achieved when the underlying basis of the particular entity is determined. This is usually accomplished by the recognition of a chromosome abnormality, familial occurrence (suggesting a certain Mendelian basis), a disease-causing gene mutation, or a well-characterized environmental etiology.

Now let us return to Hennekam's Commentary. Recent advances in molecular biology have provided clarity and insight into many aspects of malformation syndromes, but, as suggested by Hennekam, have created new challenges. (See Figure 1 in his Commentary). For example, the exact same mutation of the *FGFR2* gene has been observed to cause Crouzon syndrome in one patient and Pfeiffer syndrome in another. Another example consists of the recognition that certain well established syndromes are now known to be caused by several different genes (e.g. Bardet-Biedl syndrome is now known to be caused by at least 13 different genes). A third

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example is also a common story in recent years: different mutations in a particular gene can causes several different previously well established phenotypic entities (e.g. mutations in *COL2A1* produce at least seven different discrete entities including Stickler syndrome, Kniest syndrome, etc.). So now in diagnosing these syndromes do we simply call this latter group of conditions the type 2 collagenopathies and leave it at that? No, of course not. The natural history and clinical outcome of these various well-characterized phenotypes are quite different. Do we simplify the issue by stating that there is a "spectrum" or continuum? Again, no; we have to take into account both the specific phenotype of the patient and the particular genotype in our counseling and guidance for the patient and family (see the recommendation by Robin and Biesecker to use a multiaxis nomenclature system for this scenario[11]).

Proposal: Reconvene an international working group on terms: the dilemma described here and detailed by Hennekam in his provocative paper has led me to propose that an International Working Group should convene and revisit the definitions of the terms and nomenclature in morphologic defects. In particular, the definitions of syndrome, sequence, association, polytopic field defect and spectrum should be clarified in light of the molecular advances of the last two decades. The term sequence is often used interchangeably with developmental field defect; the distinction needs clarification in the literature. I would assert that we have reached a new era in the clinical delineation of birth defects.

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