

Commentary

Terminological Inexactitude

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My title comes from an apposite coinage of Winston Churchill's in a speech to the House of Commons on February 22, 1906. Linguists and laymen alike have argued for centuries about "growth" and "degradation" of the language, any language. Linguists describe two camps: *prescriptivists* and *permissivists*. The former argue for law and order to stop civilization's slide down the drain. The latter hold that the language will and should evolve freely. Historically, the permissivists have always been ascendant; language evolution is like the weather, it will change and there is not much one can do about it. I waver without cease between the two camps. In the spoken language, most of us lean to the permissivist view. But, we should recognize that in some situations more care is needed.

"When I use a word," Humpty Dumpty said, in a rather scornful tone, "it means just what I choose it to mean—neither more nor less."
"The question is," said Alice, "whether you can make words mean so many things."¹

In formal writing, we tend to be more careful in our choice of words. It is here that I find myself in the prescriptivist camp and argue that the use of proper terminology is important for clear communication.

One case where imprecision of language causes a problem is how we label instances of multiple malformations in a single individual. In English writing, to avoid serial repetition of a word, we are taught to use synonyms. Since *syndrome* and *association* are both used to label multiple malformation complexes, they are sometimes mistakenly used as synonyms. Michael Cohen has summarized and extensively discussed the recommendations of an international working group for improvements in the terminology of birth defects (hereafter called the recommended terminology), particularly the naming of multiple defects in the same individual [Spranger et al., 1982; Cohen, 1997]. In common

usage, *syndrome* is variously defined as "a group of signs and symptoms that occur together and characterize a disease" [Webster's New Collegiate Dictionary, 1950], "a group of symptoms that collectively indicate or characterize a disease, or another abnormal condition; a complex of symptoms indicating the existence of an undesirable condition or quality" [American Heritage Dictionary, 1992], or "a group of symptoms or pathological signs which consistently occur together, especially with an (originally) unknown cause; a condition characterized by such a set of associated symptoms" [New Shorter Oxford English Dictionary, 1993]. These definitions are fine but evade an element of precision that seems warranted by the development of understanding in the field of dysmorphology. *Syndrome* comes from the Greek *sundromos* ("running together"). The question is, why are they running together? The answer should be because they have the same cause. Accordingly, the recommended terminology includes a restricted definition of the word *syndrome* to specify it as multiple anomalies, thought to be pathogenetically related and not representing a sequence. *Sequence* is the term applied to multiple defects derived from a single known or presumed antecedent structural defect. Another, conceptually related, term used for multiple anomalies is *field defect*, or those anomalies resulting from the perturbation of an embryonic locus or developmental field that is destined to give rise to various structures. Opitz [1986] has discussed the developmental field concept in depth, and his commentary should be reread periodically. Yet other examples of multiple malformations are designated as *associations*. An *association* is defined as a nonrandom occurrence of several morphological

¹Lewis Carroll, *Through the Looking Glass*, Chapter 6.

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defects not identified as a sequence or a syndrome. Left unsaid is the possibility of “none of the above.”

While the term *association* was proposed as a statistical concept, that is, a “nonrandom” occurrence of several morphological defects, the defects included within associations have not always been established to be nonrandomly associated—sometimes that judgment is rather subjective or based on a sample size too small to be genuinely valid. However that may be, I think the terminology, despite being loosely used, serves at least three functions: (1) it is a shorthand list of findings, (2) it is a reminder to look more diligently for possibly concurrent abnormalities, and (3) it is a clue to the researcher that etiologic investigation may be fruitful. But please, an association is not a diagnosis in terms of causation—it is a description.

Should we bother to reserve the designation *syndrome* for those conditions of known or presumed known etiology? Let me use the VACTERL (or VATER) association as a case in point. It has been common for that label to be applied when three or more of the specified defects are found in one individual. But consider that at least 31 known-genesis syndromes in Smith's Patterns of Human Malformation could thus be described as examples of the VACTERL association [Jones, 1997]. In fact, one, trisomy 18, may have all seven components. Surely we would not accept labeling these conditions as “VACTERL syndrome.”² It should be noted that for any combination of multiple anomalies, just as for isolated anomalies, there typically will be multiple etiologies.

Consider the transmogrification of the CHARGE association. Based on original observations by Hall [1979] and Hittner et al. [1979], the pattern of findings was categorized as an association by Pagon et al. [1981]. Tellier et al. [1998] reported their findings among 47 cases of CHARGE association but applied the name CHARGE syndrome. Vissers et al. [2004] and subsequently Lalani et al. [2006] and Jongmans et al. [2006] found that 61% (133 of 217) CHARGE patients had mutations in the CHD7 gene. Because a cause was identified, this seemed to justify a name change to the CHARGE syndrome [Carey, 2005]. However, the 39% without the gene mutations were now what—CHARGE association or CHARGE syndrome? Consulting the relevant OMIM [2007] entry (#214800) reveals confusion. “CHARGE syndrome” is used 19 times, “CHARGE association” 15 times, “CHARGE” (alone) four times, “CHARGE patients” twice, and “CHARGE complex,” “CHARGE constellation,” “the mnemonic CHARGE,” and “the term CHARGE” once each.

There is a way out of this dilemma. When an etiology is found for some of the cases initially included in an association, that group should be relabeled with a distinct and descriptive name that clearly separates it from the association. To his credit, Graham [2001] commented on the “recognizable syndrome within the CHARGE association” and proposed the name Hall–Hittner syndrome. The discovery of a cause for some cases means that only one syndrome has been identified; the rest of the conglomerate does not become a syndrome, it remains an association. To use the same name for both is not helpful.

I think some of the confusion arises because “why” and “how” are not the same question. In common usage there is ambiguity in the words “cause,” “origin,” “etiology,” and even “why.” Often when we use these words we include not only the initiating factor but also the process that follows. There is less ambiguity in the word “how.” Here we are more clearly addressing the question of process. If we are careful in our use of terminology, “why” is a query about cause, and “how” is a query about the way(s) that cause produces an abnormality. I recall James G. Wilson teaching some years ago that the sequence in teratology was *cause, mechanism, pathogenesis, and manifestation*. *Cause* was the initiating factor, *mechanism* was what happened at the (usually) subcellular level, *pathogenesis* was what could be observed of the process macroscopically, and *manifestation* was what we end up recognizing as an abnormality. I have found it useful to use this sequence in exploring the origin and nature of abnormalities.

Applying these concepts to the terminology recommended by the working group, only *syndrome* and *association* speak to cause; *sequence* and *field defect* deal with the question of “how” or the mechanism/pathogenesis of defects. *Syndrome* posits a known (or perhaps strongly suspected) cause; I would further specify it should be a *single* cause. On the other hand, *association* suggests, “these manifestations may be causally related, but we do not know how, and several causes may be operative within this grouping.”

I do urge the careful use of the terminology recommended by Spranger et al. [1982]. In a time when we are making real gains in our knowledge of the causation of birth defects, I think it is especially important to distinguish between what we know and what we have yet to learn. That we now know different mutations in the same gene may result in different phenotypes, while mutations in different genes may result in apparently similar phenotypes, I take as a message that care in naming is warranted. We may name a condition for its appearance, for its etiology, for its functional aberration, for its first describer, or for more obscure reasons. Whatever name is chosen, implicit in the qualifier *syndrome*

²I have seen it written as “Vater syndrome,” suggesting perhaps that it is a condition first described by Emil Ludwig Vater (who presumably later changed his name to Vacterl).

should be the notion that we know the etiology. I think it is useful to have the qualifier *association* to signal that we do *not* know the etiology. Otherwise, to use *syndrome* for instances of associations implies that we know something of the etiology, or that all cases have more similarity than may actually be the case. Accordingly, syndromes and associations should be given different and distinct names to avoid confusion.

My 35-year experience of detailed examinations of fetuses and neonates tells me that there are many instances of multiple defects that currently defy etiologic explanation or meaningful labeling. They are reminders of how much we have yet to learn. I believe that the *syndrome-association* and *sequence-field defect* terminology is useful, particularly as it signals the extent and limitation of our knowledge. I worry that use of imprecise terminology may lull us or others into thinking we know more than we really do. I have no illusions about changing the way people talk, but at an editorial level we can emend the literature to maintain more precision in the use of our selected terminology.

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