TO THE EDITOR: We just witnessed an interesting debate, with lowdown punches, on the potential role of airway smooth muscle (ASM) in asthmatic airway hyperresponsiveness (AHR) when the ASM proponents Drs. Gunst and Panettieri faced the ASM opponents Drs. Paré and Mitzner (2). However, part of the disagreement seems to lie upon the vocabulary used. On one hand, the proponents reported that several molecules that are overexpressed in asthma have the ability to affect ASM contractility. IL-17A can now be added to this list (3). These observations suggest that the contractile properties of ASM are malleable. In asthmatic lungs, where the ASM is bombarded by many of those molecules, it seems reasonable to infer that the ASM may become stronger, stiffer, quicker, and/or less likely to relax, which may all contribute to AHR. On the other hand, the opponents can argue that non-asthmatic ASM would behave similarly under these aberrant circumstances. Therefore, the ASM of asthmatics is not abnormal. The term “alterations” in the title of this debate is a source of ambiguity, because it can either mean that the alterations are innate (genetically determined) or acquired due to both the abnormal environment in which asthmatic ASM operates and the recognized malleability of ASM contractility. If my little 10 years of experience is worth anything, I don’t think there is convincing evidence of innate differences in contractility between asthmatic and non-asthmatic ASM in humans. The hypercontractile phenotype observed by Ma et al. (4), Matsumoto et al. (5), and more recently Sutcliffe et al. (6) in isolated cells could have been acquired and simply maintained in culture; not mentioning that those findings are plagued with the lack of consistency (1).

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TO THE EDITOR: In an intriguing discussion about phenotype of airway smooth muscle (ASM) among asthmatic patients and airway hyperresponsiveness (AHR), inflammation is the central highlight on its role in the pathophysiology of ASM and AHR (4, 6). Originally, there could be a number of inflammatory mediators involved in ASM phenotype changes and AHR, the cyclooxygenase (COX) pathway is one of them (5). The terminal prostaglandins (PGs) generated by inflammatory cascade mediated by COX enzyme catalyzing arachidonic acid (AA) should be considered in altering ASM phenotype and possibly in AHR. Prostaglandin E2 (PGE2) and its receptors have been demonstrated to be involved in ASM phenotype changes and its relaxation (3). Similarly, PGE2 seems to regulate intracellular 3'-5'-cyclic adenosine monophosphate (cAMP), which governs multiple aspects of ASM function (2). Again, the airway smooth muscle proliferation (6) could be regulated by PGE2 as well. It is likely that the COX pathway may produce both smooth muscle relaxant (PGI2 and PGE2) and contracting PGs, i.e., thromboxane A2 (TxA2) and PGF2 (PGF2) in ASM cells (5) as they do in vascular smooth muscle cells. Hence, the ASM phenotype could be dependent on the COX-mediated inflammation, and AHR might be in intricate balance of these contrasting PGs. Therefore, an understanding about the role of PGs and their specific receptors in ASM will be an immensely important aspect to identify novel therapeutic targets and to develop newer drugs for the treatment and prevention of asthma (1).

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ON THE ONE HAND, ON THE OTHER HAND
TO THE EDITOR: Since the definition of phenotype is “the observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences,” it could be argued that both approaches in these two articles are correct—one “pointing the finger” at intrinsic abnormalities and the other ascribing “blame” to the environment or milieu. Another point in favor of a “both have merits” response is that each group of authors has been even handed in their citing of articles from our group—8/45 in the case of Drs. Gunst and Panettieri (3) and 7/32 from Drs. Paré and Mitzner (4). This displays an admirable and equal appreciation of critical aspects of the literature by both sets of combatants!

Two points in the Paré/Mitzner article provoke comment. First, they describe maximal shortening in airway smooth muscle cells from asthmatic subjects as 25–49% of initial length and state that this is much less than that of the maximal shortening of “human airway smooth muscle strips—75%” (1). This displays an admirable and equal appreciation of critical aspects of the literature by both sets of combatants!

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critical cells in asthma. For instance, in addition to exhibiting
fundamental intrinsic abnormalities relating to AHR such as
altered calcium homeostasis (6), asthmatic ASM can influence
its milieu by directly recruiting mast cells (2) whose adhesion
is increased in asthma (3). Mast cells then stimulate ASM,
which in turn recruit additional mast cells, thus generating an
auto-activation loop (2). Conversely, another important struc-
tural cell in the milieu in asthma, the epithelial cell, influences
ASM. Indeed, we recently demonstrated that epithelium-de-
derived YKL-40 increased ASM proliferation and migration,
particularly using asthmatic ASM cells (1). Therefore, the
actual question our experienced although enthusiastic col-
leagues should now deal with, is how much of AHR should be
ascribed to ASM phenotype and how much to the milieu, i.e.,
acting as talented physiologists, moving from a qualitative to a
quantitative issue.

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AIRWAY HYPERRESPONSIVENESS—AN IMPORTANT
PHENOMENON WITH UNCLEAR MECHANISMS

TO THE EDITOR: Asthmatics suffer from recurrent exacerbations
of airway narrowing. Directly linked to this problem is airway
hyperresponsiveness (AHR), a parameter that rather easily can
be measured in these patients. However, still we don’t know
the mechanisms behind AHR. One fundamental question is
how much alterations of the airway smooth muscle (ASM)
function is involved the development of AHR. In this issue of
the Journal of Applied Physiology two research groups give an
insight of today’s knowledge discussing the pros and cons of
this issue (2, 5). Both groups agree that are no direct evidence
that alterations of the ASM function are involved in the
involvement of AHR. However, when studying the scheme
described by Paré and Mitzner (5), who defend the hypothesis
that ASM not is involved, it can be concluded that ASM has
the possibility to influence all parameters that leads to in-
creased airway narrowing. Parallel findings provide compelling
evidence that ASM is a plastic tissue that responds with
altered function to environmental changes (2, 4) and especially
those that show both an increased contractile capacity (3, 6)
and increased response to contractile mediators induced by
inflammation (1). Thus because AHR is a measurement of
ASM contraction and the contractility of ASM can be in-
creased during inflammatory conditions, everything points to
ASM being of major importance in the development of AHR.
Indeed, to find new therapies for asthmatic patients, more
research needs to focus on the mechanisms behind AHR
because it both can lead to findings of targets and provide new
understanding of the underlying inflammatory processes.

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