This Week's Citation Classic®

Somlyo A P & Somlyo A V. Vascular smooth muscle. I. Normal structure, pathology, biochemistry, and biophysics. *Pharmacol. Rev.* 20:197-272, 1968.
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This paper was intended to be a comprehensive review of the ultrastructure, biochemistry, and physiology of smooth muscle with an emphasis on general, cell-physiological aspects and pathophysiological significance. (Part II of the article, published in 1970, covered pharmacology.) The then-controversial concept of pharmacomechanical coupling as a physiological mechanism was disseminated through this review. [The *SCI*® indicates that this paper has been cited in over 640 publications.]

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Science is not a branch of show business, or so we were brought up to believe, and the feigned surprise fashionable at Oscar ceremonies seems inappropriate in discussing a *Citation Classic*. Indeed, hope, if not anticipation, that a manuscript will have above-average influence on a field is probably not unknown among authors of *Citation Classics*.

We had some such hope when, prompted by Paul Bianchi, we wrote our review of smooth muscle, a subject that we had chosen as our major research interest. This choice was our second major decision, the first having been to get married. The importance of smooth muscle in physiology and in pathology (for example, in atherosclerosis and hypertension) was then exceeded only by our profound ignorance and curiosity about the basic mechanisms of smooth-muscle function. This timely recognition of the obvious, evidenced by the subsequent growth of the field, undoubtedly contributed to the popularity of our review. We made an effort to be both comprehensive and critical: the nearly 1,000 references covered, to the best of our knowledge, most of what had been published and known about the structure, ultrastructure, biochemistry, and cell physiology of smooth muscle. A lesson learned later—one that we try to remember now as editors or referees—is that lack of personal experience with a given technique can lead to critical errors in assessing the work of others.

The introduction of the concept of pharmacomechanical coupling, the classification of smooth muscles into phasic and tonic, and the definition of some major research problems may also have contributed to the review's citedness.

Pharmacomechanical coupling is a class of excitation-contraction coupling mechanisms that can trigger contraction or relaxation of smooth muscle independently of changes in cell-membrane potential; the idea that it can operate in normal smooth muscle was based on an experimental paper of ours[1] that brought into the realm of physiology an earlier observation[2] indicating that completely depolarized smooth muscles could be contracted by drugs. Having initially met some resistance, the physiological importance of pharmacomechanical coupling has since been verified by many laboratories (including those of Casteels, Coburn, and Kuriyama), and inositol-1,4,5-trisphosphate[3] has recently been implicated as the major messenger of pharmacomechanical calcium release.[4] The classification of smooth muscles into phasic and tonic ones, based on the shape of contraction following depolarization (in analogy with striated muscle), has acquired the supreme accolade of not being cited due to obliteration by usage. Authors who now employ it are probably unaware of either its relatively recent origins or E. Bozler's earlier "single unit" and "multiunit" classification.[5]

To paraphrase Samuel Johnson, "The knowledge of having your ignorance hung out in public wonderfully concentrates the mind." Hence, the review also contributed to defining our own research aims, as we became very much aware of such outstanding questions as "How is myosin organized?" and "What are the cellular sources of activator calcium in smooth muscle?" Subsequently our laboratory played a role in answering some of these questions by identifying myosin filaments in resting and in contracted smooth muscle[6] and by establishing the sarcoplasmic reticulum as the major intracellular source of activator calcium.[7] In search of direct methods, we were led on an exciting journey through electron microscopy, electron probe analysis, and, more recently, electron energy-loss spectroscopy.

We have occasionally been prodded for an "encore" but have not the temerity to do one, given the technical sophistication and sheer proliferation of current literature. Multiauthored texts are devoted today to subjects that could once be covered by two authors, in a few pages of a *Citation Classic* now covered by "les neiges d'antan (the snows of yesteryear)."

1. **Somlyo A V & Somlyo A P.** Electromechanical and pharmacomechanical coupling in vascular smooth muscle. *J. Pharmacol. Exp. Ther.* 159:129-45, 1968. (Cited 315 times.)
2. **Evans D H L, Schild H O & Thesleff S.** Effects of drugs on depolarized plain muscle. *J. Physiol.—London* 143:474-85, 1958. (Cited 255 times.)
3. **Berridge M J & Irvine R F.** Inositol trisphosphate, a novel second messenger in cellular signal transduction. *Nature* 312:315-21, 1984. (Cited 1,180 times.)
4. **Walker J W, Somlyo A V, Goldman Y E, Somlyo A P & Trentham D R.** Kinetics of smooth and skeletal muscle activation by laser pulse photolysis of caged inositol 1,4,5-trisphosphate. *Nature* 327:249-51, 1987.
5. **Bozler E.** Conduction, automaticity, and tonus of visceral muscles. *Experientia* 4:213-8, 1948. (Cited 220 times since 1955.)
6. **Somlyo A V, Butler T M, Bond M & Somlyo A P.** Myosin filaments have nonphosphorylated light chains in relaxed smooth muscle. *Nature* 294:567-70, 1981. (Cited 55 times.)
7. **Somlyo A P.** Excitation-contraction coupling and the ultrastructure of smooth muscle. *Circ. Res.* 57:497-507, 1985.

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