

Correspondence

Slow reactive substance of anaphylaxis

To the Editor:

For the Journal's September 2009 thematic issue on "Mechanisms of Allergic Disease," Austen et al¹ contributed a welcome extensive review of the pathologic implications of leukotriene E₄. The introduction of their coverage traces identification of slow reactive substance of anaphylaxis to the 1960 report of Brocklehurst.² In an evaluation of the subject 20 years earlier, Austen³ dated recognition of elaboration of a substance responsible for sluggish contractile response of smooth muscle during anaphylactic challenge to the 1940 finding of Kellaway and Trethewie.⁴ Neither of the 2 scholarly reviews noted the first documented detection of a slow reactive contractile phenomenon described independently by Harkavy⁵ in 1925. However, his omission is not entirely unexpected because the seminal publications of Kellaway and Trethewie⁴ and Brocklehurst²—whether they overlooked it, were unaware of it, or disregarded it—neither cited nor referred to the reports of Harkavy's earlier work.

Joseph Harkavy (1890-1980; Fig 1), after receipt of an MD from Cornell University Medical College in 1914, spent his entire professional career on the staff of Mount Sinai Hospital in New York creating and developing a section on asthma and allergic disease. His dedicated tenure was interrupted only by a fellowship from 1924 to 1925 in European medical centers: with Bancroft in physiology at Cambridge, Aschoff in pathology at Friburg, and Storm van Leeuwen in allergy at Leiden. In 1925 while at the Leiden Institute of Pharmacology, in well controlled experiments using the Schultz-Dale technique, he discovered the presence of a substance in the sputum of patients with asthma that caused spasms of isolated rabbit and cat uterine muscle strips. Although the nature of the responsible substance was not elucidated, patterns of recorded contractions—in some instances prompt, spasmatic, and sustained, and in others sustained for longer periods of up to 5 to 7 minutes—suggested the actions of both histamine and what later would be defined as slow reactive substance of anaphylaxis,² respectively. On Harkavy's return to New York, his follow-up studies at Mount Sinai Hospital confirmed the initial finding of slow contractile reactions of smooth muscle associated with asthmatic pathology⁶ (Fig 2). Whether these reports furnished leads for Kellaway and Trethewie and for Brocklehurst to ascertain the character of the detected substance and its significance in asthma and allergic reactivity is not known.

The professional career of one of us (S.G.C.) overlapped with that of Harkavy. Thus, there were occasions and opportunities for our paths to cross, to interact, and to learn of his pioneering endeavors at first hand. As an astute observer, Harkavy was considered ahead of his time in observations that called attention to findings that could not be analyzed until many years later. In addition to the first detection of a slow reactive smooth muscle constrictor agent, his original descriptions included hypersensitivity to tobacco, especially as a factor in thrombophlebitis obliterans and migrating phlebitis; and the disorder of asthma with eosinophilia, recurrent eosinophilic pulmonary infiltrations, and polyserositis as a variant of Kussmaul-Maier syndrome (periarteritis nodosa), which for many years was known in the medical literature as Harkavy syndrome.⁷ With subsequent

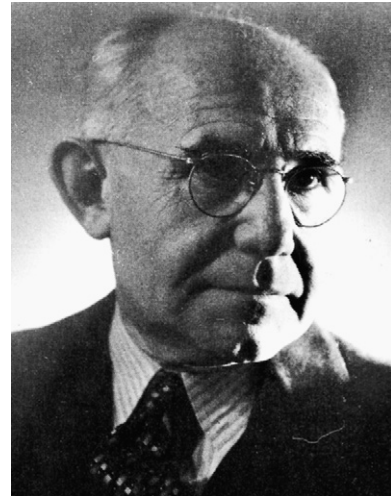


FIG 1. Joseph Harkavy, MD.

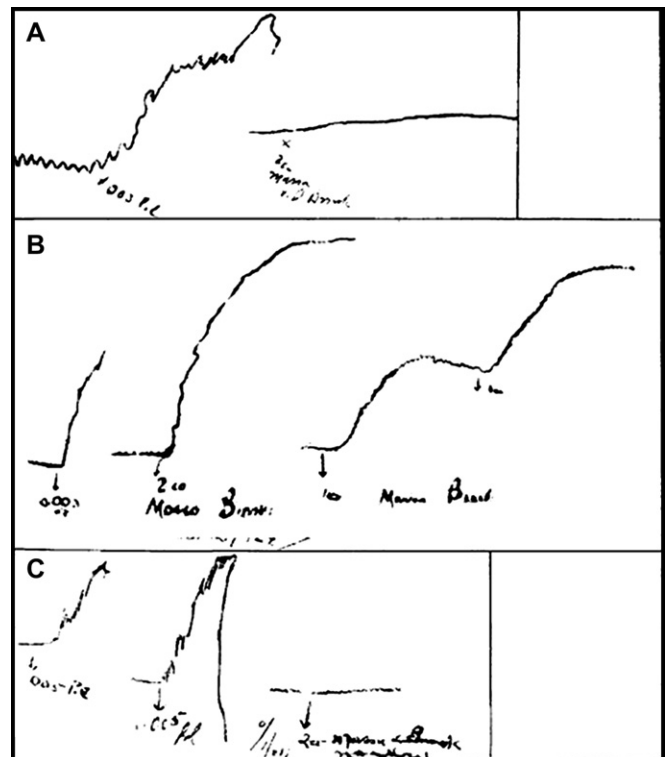


FIG 2. Kymographic tracing depicting slow reactive contraction of a smooth muscle strip challenged by extract of sputum from patient sensitive to oat infested by mites. An intradermal skin test evoked a severe asthmatic attack that enabled recovery and study of the patient's sputum before, during, and after the attacks. Note flat curve of the muscle before (A), pattern of spasm and contraction during (B), and return to a negative curve after (C) the attack had subsided. Reprinted with permission from p. 644, Harkavy J. Spasm-producing substance in the sputum of patients with bronchial asthma. *Arch Intern Med* 1930;45:641-6.⁶

classification of the vasculitides, its component features were incorporated into the redefined entities of Churg-Strauss allergic granulomatosis, systemic necrotizing vasculitis, and hypersensitivity polyarteritis.

If Austen and his predecessors were concerned only with limited physical characteristics and chemical properties of the slow reactive substance of anaphylaxis, then their excluding or bypassing Harkavy's published reports—whether inadvertently or by design—can be understood. Nonetheless, in our opinion, Harkavy's original description of the slow reactive contractile phenomenon is historically noteworthy and merits recall of chronologic priority as a landmark in the progressive uncovering of knowledge of anaphylactic, allergic, and asthmatic mediators of hypersensitivity.

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