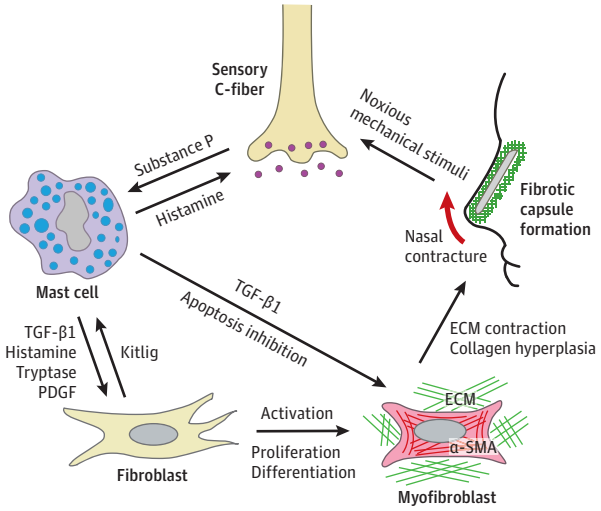
Figure 2. Putative Neuropeptide–Mast Cell–Myofibroblast Signaling Pathway



Surgery-induced injury activates mast cells and fibroblasts by neuropeptide signaling. In at-risk patients, persistent noxious and mechanical stimuli caused by the presence of a silicone prosthesis results in continued neuropeptide synthesis and chronic activation of myofibroblasts. Over time, collagen hyperplasia and extracellular matrix (ECM) contraction result in nasal contracture. α-SMA indicates alpha-smooth muscle actin; PDGF, platelet-derived growth factor; and TGF-β1, transforming growth factor-beta 1.

years). No significant differences between the groups were found in the baseline data.

The CC group showed a higher level of SP than did the NCC group did. All capsules in the CC group showed positive SP staining to various degrees (2 of grade +2 and 1 of grade +1; $P < .01$, linear by linear association). Two of 9 capsules in the NCC group showed low-intensity SP staining (grade +1) and the other 7 showed negative findings. However, mast cell and neutrophil counts and staining grades of the myofibroblasts were not significantly different between the 2 groups.

Discussion | In this study, SP immunoreactive staining was stronger in the CC group than in the NCC group. Similarly, elevated levels of SP have been observed in various fibrotic conditions.[3] Mast cells and fibroblasts are exposed to activating signals during a surgery-induced injury. Under normal conditions, numbers of fibroblasts, myofibroblasts, and mast cells diminish as healing progresses. However, persistent mechanical stimuli caused by the silicone prosthesis can result in persistent neuropeptide synthesis and chronic fibroblast and mast cell activation. Although significant associations were not found between SP and numbers of mast cells in our study, SP has been called a *mast cell secretagogue*.[4] Substance P also stimulates fibroblast proliferation and impairs proapoptotic signaling in myofibroblasts.[5] Mast cell–derived histamine causes the release of SP from type-C unmyelinated nerve fibers.[6] Substance P, in turn, potentiates histamine release. Thus, fibroproliferative stimuli persist and escape regulatory control. As mast cells and fibroblasts are activated, a cycle is engaged. These events create an environment of sustained myofibroblast hyperplasia, resulting in disorganized collagen deposition (**Figure 2**).

Owing to its small sample size, our report must be considered preliminary. Although our evidence supports a neuroinflammatory axis as the mechanism underlying capsular contracture, further studies with additional biomarkers and larger groups of patients may reveal more information about the pathogenesis of capsular contracture.

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Accepted for Publication: February 4, 2017.

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Published Online: July 13, 2017. doi:10.1001/jamafacial.2017.0207

Author Contributions: Drs Sunwoo and Jin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sunwoo, Kim, Jin.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Sunwoo, Jung, Kim.
Critical revision of the manuscript for important intellectual content: Sunwoo, Kim, Jin.
Statistical analysis: Sunwoo, Jung, Kim.
Administrative, technical, or material support: Jung.
Study supervision: Jin.

Conflict of Interest Disclosures: None reported.

1. Jung DH, Moon HJ, Choi SH, Lam SM. Secondary rhinoplasty of the Asian nose: correction of the contracted nose. *Aesthetic Plast Surg*. 2004;28(1):1-7.

2. Park JH, Mangoba DCS, Mun SJ, Kim DW, Jin H-R. Lengthening the short nose in Asians: key maneuvers and surgical results. *JAMA Facial Plast Surg*. 2013;15(6):439-447.

3. Ogawa R. Keloid and hypertrophic scarring may result from a mechanoreceptor or mechanosensitive nociceptor disorder. *Med Hypotheses*. 2008;71(4):493-500.

4. Foreman JC. Substance P and calcitonin gene-related peptide: effects on mast cells and in human skin. *Int Arch Allergy Appl Immunol*. 1987;82(3-4):366-371.

5. Jing C, Jia-Han W, Hong-Xing Z. Double-edged effects of neuropeptide substance P on repair of cutaneous trauma. *Wound Repair Regen*. 2010;18(3):319-324.

6. Kulka M, Sheen CH, Tancowny BP, Grammer LC, Schleimer RP. Neuropeptides activate human mast cell degranulation and chemokine production. *Immunology*. 2008;123(3):398-410.

COMMENT & RESPONSE

Importance of Reporting Duration of Facial Paralysis in Studies of Emotion and Well-being

To the Editor We are grateful for the recent publication from Johns Hopkins University bringing attention to the association among facial paralysis (FP), depression, and quality of life. Nellis et al[1] found that 42.1% of patients with facial paralysis

screened positive for depression, having significantly higher Beck Depression Inventory scores than control patients. Those with a worse degree of paralysis (House-Brackmann grade ≥3) were significantly more likely to screen positive when controlling for female sex. Absent from logistic regression analysis was paralysis duration. Although the authors acknowledge this limitation, we wish to elaborate on the importance of measuring duration of FP. It is plausible that duration moderates the effect of FP on depression. We suggest this is related to the tendency to mispredict the impact of present and future emotion states on well-being.

As demonstrated in the affective forecasting literature, people typically overestimate the impact of major life events that involve a negative outcome or consequence, and underestimate the positive impact of other events (eg, recovery or family support) will have on their emotional states.[2,3] As a result, people fail to accurately predict their future well-being and tend to overestimate the emotional impact that an important life change, such as a chronic illness or disability, will have on their daily life satisfaction.[2] Individuals who have recently experienced FP may be particularly likely to mispredict their future emotional states by overestimating both the intensity and duration of their negative reactions toward FP-related circumstances on self-report measures, including assessments of life satisfaction and depression. As patients experience longer durations of FP, their predictions may show better calibration owing to experience with the condition.

The existing literature on FP and duration is limited. Fu and colleagues[4] found significant associations between longer duration of FP and Hospital Anxiety and Depression Scale depression scores ($\rho = 0.224$; $P < .05$). Question ordering of severity and duration, however, may have influenced self-reported depression scores by bringing to mind negative aspects of the condition, or focusing attention on their condition when self-reporting ratings of depression, despite disease acceptance gained from a longer illness duration.

Conversely, Bogart and Matsumoto[5] found adults with lifelong FP from Moebius syndrome (mean [SD] age, 37.73 [13.70] years) did not significantly differ from age- and sex-matched controls in measurements of anxiety, depression, or life-satisfaction.

Given a longer duration of illness, will adults with acquired FP adapt similarly to those with congenital paralysis? Future research that includes duration of FP may help answer this question.

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Published Online: June 15, 2017. doi:10.1001/jamafacial.2017.0846

Conflict of Interest Disclosures: None reported.

1. Nellis JC, Ishii M, Byrne PJ, Boahene KDO, Dey JK, Ishii LE. Association among facial paralysis, depression, and quality of life in facial plastic surgery patients [published online December 8, 2016]. *JAMA Facial Plast Surg*. doi:10.1001/jamafacial.2016.1462

2. Ubel PA, Loewenstein G, Schwarz N, Smith D. Misimagining the unimaginable: the disability paradox and health care decision making. *Health Psychol*. 2005;24(4S):S57-S62.

3. Wilson TD, Gilbert DT. Affective forecasting: knowing what to want. *Curr Dir Psychol Sci*. 2005;14(3):131-134. doi10.1111/j.0963-7214.2005.00355.x

4. Fu L, Bundy C, Sadiq SA. Psychological distress in people with disfigurement from facial palsy. *Eye (Lond)*. 2011;25(10):1322-1326.

5. Bogart KR, Matsumoto D. Living with Moebius syndrome: adjustment, social competence, and satisfaction with life. *Cleft Palate Craniofac J*. 2010;47(2):134-142.

In Reply We appreciate Chaiet and Carpenter's thoughtful contribution regarding our recently published article "Association Among Facial Paralysis, Depression, and Quality of Life in Facial Plastic Surgery Patients."[1]

It has generally been assumed that individuals with facial deformity experience emotional distress. However, prior studies did not specifically measure emotional distress in patients with facial paralysis. Thus, our prospective study focused on measuring depression and quality of life (QOL) in patients with all-cause facial paralysis compared with control patients. For the purposes of our proof of principle study, the first of its kind, we aimed to determine if there was an association among facial paralysis, depression, and QOL. This pilot study served as a means to provide a foundational understanding. This set the stage for future studies that may investigate the extent of disease duration on patient-reported psychosocial measures.

Chaiet and Carpenter suggest that duration of FP has an impact on QOL and depression. Interestingly, prior studies examining the impact of disease duration on health states reveal conflicting findings. Furthermore, to our knowledge, a study specifically evaluating the relationship between psychological health and facial paralysis duration has not been performed. Sackett and Torrance[2] maintain that the mean daily health state utility, including social and emotional outcomes, dramatically worsens as the duration of the corresponding health state persists. Almeida et al[3] noted that patients with a chronic disease state, such as diabetes, demonstrate a nonlinear relationship between depression and duration of disease showing an improvement followed by an ultimate worsening of depression in the long term. Fu et al[4] found a correlation between duration of facial paralysis and depression, although this cross-sectional study was limited by a large nonrespondent rate and did not include a control group.

Chaiet and Carpenter raise concerns that patients overestimate negative future outcomes, and they suggest that similarly patients with facial paralysis may overestimate potential negative reaction, or "impact bias." However, our study did not assess the future state. Rather, we assessed the patients' current psychological state. Furthermore, the article by Ubel et al[5] that Chaiet and Carpenter reference speaks to the "disability paradox," in which a patient with an illness is more likely to report a higher well-being compared with the well-being a healthy individual would estimate if they developed the corresponding illness. Thus, it is possible that the effect of facial

paralysis on QOL and depression may be even larger than demonstrated in our study results. Furthermore, Moore et al,[6] in their study examining the correlation among depression, QOL, and time, showed that depression significantly lowers a person's present and future perceived QOL. Thus, individuals who screen positive for depression may behave differently compared with the general population in affective forecasting.

In conclusion, we appreciate the question raised by Chaiet and Carpenter about the impact of duration on perceived QOL and depression in patients with facial paralysis. While the current data on the impact of disease duration on perception are conflicting, perhaps future studies will help clarify. The relationship among facial paralysis, depression, and QOL identified in our study serves as foundation on which to design future experiments to address additional variables.

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Published Online: June 15, 2017. doi:10.1001/jamafacial.2017.0849

Conflict of Interest Disclosures: None reported.

1. Nellis JC, Ishii M, Byrne PJ, Boahene KDO, Dey JK, Ishii LE. Association among facial paralysis, depression, and quality of life in facial plastic surgery patients [published online December 8, 2016]. *JAMA Facial Plast Surg*. doi:10.1001/jamafacial.2016.1462

2. Sackett DL, Torrance GW. The utility of different health states as perceived by the general public. *J Chronic Dis*. 1978;31(11):697-704.

3. Almeida OP, McCaul K, Hankey GJ, et al. Duration of diabetes and its association with depression in later life: the Health In Men Study (HIMS). *Maturitas*. 2016;86:3-9.

4. Fu L, Bundy C, Sadiq SA. Psychological distress in people with disfigurement from facial palsy. *Eye (Lond)*. 2011;25(10):1322-1326.

5. Ubel PA, Loewenstein G, Schwarz N, Smith D. Misimagining the unimaginable: the disability paradox and health care decision making. *Health Psychol*. 2005;24(4S):S57-S62.

6. Moore M, Höfer S, McGee H, Ring L. Can the concepts of depression and quality of life be integrated using a time perspective? *Health Qual Life Outcomes*. 2005;3:1.