

Historical Review

The correspondence and collaboration of Harvey Cushing and Irvine Page: Lessons from the Cleveland Clinic Archives

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Abstract

Harvey Cushing is well-known as a pioneer of brain surgery and is considered the father of modern neurosurgery. However, Cushing's interests and contributions extend beyond neurosurgery. Through his determined interdisciplinary collaboration in medicine and biomedical research, Cushing was able to contribute to numerous fields including bacteriology, anesthesiology, and endocrinology. With regards to the latter, Cushing corresponds with Irvine Page, well-known for isolating serotonin, discovering the renin-angiotensin system, and postulating of the mosaic theory of hypertension. In a correspondence spanning 3 years, from January 1933 to April 1936, Cushing and Page collaborated to discover a substance responsible for hypertension. In this historical article, the authors review the letters to highlight the collaborative efforts between leaders in disparate fields driven by the scientific curiosity. As national research agencies are focusing their funds toward collaborative and interdisciplinary research, it is interesting to note the historical communication among the scientific leaders that led to discoveries in the respective fields.

Key Words: Harvey Cushing, Irvine Page, medical history, pituitary

The concept of collaborative, interdisciplinary biomedical research is often thought of as a modern and novel mechanism to increase innovation and solve biomedical quandaries. However, the ideals of this brand of scholarship reach back to the early days of organized American medicine. In a review of institutional archives, we came across a striking example of how two giants of early American medicine corresponded to work together on a shared interest.

Harvey Cushing is widely considered the father of neurosurgery, a Cleveland native, and a great contributor to the field of endocrinology. It was this latter pursuit that led him to Irvine Page, best known for his isolation of serotonin, discovery of the renin-angiotensin system, and postulation of the mosaic theory of hypertension. At the time of the correspondence described below,

Irvine Page was a young investigator only 6 years out of his clinical internship and just 2 years fresh from a postdoctoral fellowship in a neurochemistry laboratory in Munich. Page had just begun his first official post at the Rockefeller Institute and was attempting to isolate circulating vasopressors from the blood of patients with essential hypertension. Harvey Cushing, then in the

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twilight in his career and still neurosurgeon-in-chief at Peter Bent Brigham Hospital was renowned for his work on the pituitary gland. It was the posterior pituitary, which had just become known for its production of vasopressin and oxytocin (though the effect of vasopressin was yet unclear) that led to their collaboration.

The correspondence is comprised 24 letters spanning 3 years, from January 26th, 1933 to April 25th, 1936. These letters reflect the life stages of two physician-scientists, one nearing the end of a remarkable career and the other just embarking on what would be a storied scientific journey. Of the entirety of these letters, several anecdotes are provided here as they reflect a rare window into scientific inquiry and collaboration in an era before dissemination of information was as expedient as it is today. The letters found in the Cleveland Clinic Archives start with a missed encounter-Cushing having visited the Rockefeller Institute and missing Page but also apologizing that he was unable to provide the blood of young patient of his with “basophilism” (later known as Cushing’s disease). At this time, Page was focused on finding a vasopressor substance responsible for essential hypertension, and Cushing was attempting to derive a hormonal reason for hypertension found in Cushing’s disease. Cushing wrote:^[1]

“...the only patient at hand is a young girl who has been so often punctured she is gunshy about it...but I still have high hopes for you, as it would be most important for me to know whether they have a (vaso) pressor substance.” (Cushing, January 1933).

Over the next few months, Cushing provided Page with blood samples of patients who may or may not have had Cushing’s disease in the hopes that Page would be able to identify a vasopressor substance. In June of 1933, Page mused about the general nature of hormones:^[2]

“It is not clear to my mind whether the body actually allows substances to float around in the blood freely without combining with them... if it were bound to the plasma colloids, it might be liberated at such end organs as have the power to lessen the union of the substance with the colloid...I shall be very interested to know how you feel about this.” (Page, June 1933).

It is in December of 1934 that Page excitedly enclosed a manuscript, “A syndrome occurring in patients with essential hypertension simulating diencephalic stimulation.” In this manuscript, Page described what may be serotonin syndrome. Remarkably, it would be 14 more years until he isolated serotonin at Cleveland Clinic. Cushing responded that in light of Page’s description, he regretted not having injected acetylcholine or histamine into the brain intraoperatively to determine if that was the substance that elicited the described effects. He lamented, “Someone else will have to do it now. It is,

of course, a ticklish business using one’s patients for experiments of this kind.” (Cushing December 1934).^[3]

As the correspondence wound down, Cushing moved into retirement at Yale, and the two discussed the potential for irradiation of the pituitary, in which Page proclaimed he found interest for the treatment of hypertension and asked Cushing about his experience in brain irradiation. After some brief exchanges on the potential of the brain to withstand radiation, the correspondence waned. The last note in the series is not from Harvey Cushing or Irvine Page, but from John Fulton, Cushing’s official biographer, who thanked Page for providing him a file of Cushing’s letters. It is dated November 20th, 1939, just 5 weeks after Cushing’s death.

In 1937, Page moved to Indianapolis, where he would elucidate the renin-angiotensin system, and then to Cleveland Clinic from 1945 until his retirement in 1966. During his time at Cleveland Clinic, Page would isolate serotonin and develop the mosaic theory of hypertension. Retirement did little to quiet his imagination. In 1967, convinced of the need for a national entity to help guide medical progress, and with the help of a grant from the Cleveland Foundation, he held the first meeting of what later became the Institute of Medicine.

The brief dialogs presented above are minor excerpts of communication from two physician-scientists of different fields and eras. One was a retiring neurosurgeon and the other a newly minted internist but both were brought together by a passion for scientific inquiry and a true dedication to craft and interdisciplinary collaboration. The National Institutes of Health and many other national funding agencies have in the past decade made significant strides toward encouraging and incentivizing interdisciplinary research and collaboration. The recognition that is collaborating across disparate fields is an important shift in funding priorities and mindset, but we emphasize that while incentives for collaboration is important there exists an intrinsic curiosity to solve problems by any means that may be necessary. The enclosed letters may date back nearly 80 years, but the spirit of scientific curiosity is timeless.

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Conflicts of interest

There are no conflicts of interest.

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