

This Week's Citation Classic™

Plotz C M, Knowlton A I & Ragan C. The natural history of Cushing's syndrome.

Amer J Med 13:597-614, 1952.

[Dept. Med., Columbia Univ. Coll. Physicians & Surgeons, and Edward Daniels Faulkner Arthritis Clinic, Presbyterian Hosp., New York, NY]

The findings in 33 cases of Cushing's syndrome collected from the Columbia-Presbyterian Medical Center were reported. The close parallelism of the spontaneous and the induced forms of hyperadrenalism suggested potential hazards of long-term therapy with adrenocorticotrophic hormone (ACTH) or cortisone. [The SCJ® indicates that this paper has been cited in over 365 publications since 1955.]

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In 1949 and 1950, I was a callow youth just finished with my medical residencies and my stay in the Army. I was fortunate enough to receive a Public Health Service Fellowship to Columbia-Presbyterian Medical Center and became the first rheumatology fellow of the late Charles A. Ragan, Jr. My interest, at first, was entirely in the laboratory, and I started off learning immunologic techniques from Ed Fischel. It was from this work, several years later, when I had my own laboratory and was able to persuade Jacques Singer to be my fellow, that the latex fixation test was developed.^{1,2}

In the midst of my fellowship, however, a bombshell broke upon the world of medicine. This was, of course, the discovery by Hench, Kendall, Slocumb, and Polley of the effect of compound E (cortisone) on rheumatoid arthritis.³ Instantly, the world of rheumatology became galvanized, and the worlds of endocrinology, immunology, and, indeed, all of medicine were irrevocably altered. At first, my clinical research was devoted to studying whether or not there was a deficiency of adrenal hormone in patients with rheumatoid arthritis that was being corrected by cortisone. I did some studies with George Perera that indicated that no such deficiency existed,⁴ and, indeed, this was

rapidly confirmed by many others. It soon became evident that what we were doing in treating patients with cortisone for rheumatoid arthritis was to make them hyperadrenal and that this hyperadrenalism was inextricably intertwined with the beneficial effects on the arthritis. All of a sudden, it became vital for us to understand hyperadrenalism in a better and more comprehensive way. Accordingly, I went to the medical record room and pulled the record of every patient on whom the diagnosis of Cushing's syndrome had been made at the Columbia-Presbyterian Medical Center. With the very important guidance and advice of Abbie Knowlton and, of course, under the overall supervision of Ragan, I developed as many data as I could from the quite comprehensive medical charts available to me.

It took about two years but I was able to put the data in readable and comprehensible form. Robert Loeb, who was chairman of medicine at that time, instinctively realized that the data that we would publish would be very important and that accuracy was the key. Accordingly, he had Knowlton go over everything with a fine-tooth comb so that it was checked and double-checked. Fortunately for me, in my young medical career, the data were found to be accurate! The paper has subsequently been extensively cited as the standard for naturally occurring hyperadrenalism and in papers attempting to explain the actions of the corticosteroids.

Next came the question of where to publish. The "green journal," the *American Journal of Medicine*, was edited by Alexander Gutman, whom all of us knew as a colleague at Columbia, and so he got first shot at publishing the paper. He grabbed it. This affected my whole career since not only did the article turn out to be an important one in view of burgeoning interest in hyperadrenalism, but Gutman then invited me to come to the Mount Sinai Hospital and Medical Center, where he was director of medicine, to be chief of rheumatology. It was there in my own laboratory that I did the key work that led to the latex fixation test. My whole career was thus affected by the article that has now become a *Citation Classic*.

- 1 Singer J M & Plotz C M. The latex fixation test I Application to the serologic diagnosis of rheumatoid arthritis *Amer J Med* 21 888-92, 1956 [See also Singer J M. *Citation Classic Current Contents* (S1) 21, 19 December 1977]
- 2 Plotz C M & Singer J M. The latex fixation test II Results in rheumatoid arthritis *Amer J Med* 21 893-6, 1956 (Cited 100 times.)
- 3 Hench P S, Kendall E C, Slocumb C H & Polley H F. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis Preliminary report *Ann Rheum Dis* 8 97-104, 1949 (Cited 35 times since 1955)
- 4 Perera G A & Plotz C M. The response to methacholine in rheumatoid arthritis *Amer J Med Sci* 220 307-9, 1950 (Cited 2 times since 1955)