

To Gent Zondeker  
with much frat. wish  
L. Knobil

PRESIDENTIAL ADDRESS:

Delivered at the Fifty-Ninth Annual Meeting of

The Endocrine Society

Chicago, Illinois

June 9, 1977

E. Knobil

Department of Physiology

University of Pittsburgh School of Medicine

Pittsburgh, Pennsylvania 15261

Doctor Ross, Members and Guests:

Thank you for this splendid plaque and for your overgenerous words. They are among the few, evanescent, albeit cherished, rewards of the Presidency of our Society. In sharp contrast, the punishment for succumbing to the lure of this high office is implacable, demonic, and so severe that it cannot be borne alone: the Presidential address. This year, I have attempted to lessen the shared pain by reverting to an earlier tradition of performing this annual rite in the company of a self-selected portion of the membership, suitably medicated for the occasion. This change in venue dictated the choosing of a topic less ponderous than has been customary in the recent past and, stimulated by the spectacular success of Mr. Haley's "Roots", I had set out to do a suitably brief biographical sketch of our common ancestor, Professor A.A. Berthold of Göttingen. It took much labor to discover, however, that Professor Berthold's life was no match for his brilliant experiments on cockerels which form the very basis of our Science. In fact, it was a crashing bore and so bereft of general interest that my plan to utilize his life's story as the theme of my address, no matter what the time of its delivery, had to be abandoned.

I then recalled wondering, on more than one occasion, about the identity of the first president of our Society. His name, C.E. de M. Sajous, meant nothing to me, nor to a number of others of my endocrinological generation whom I named "The Annual of the Universal Medical Sciences", which was to be an encyclopedia of the entire medical literature.

I queried. I decided, therefore, to look into the matter and discovered to my great relief and satisfaction, that I had found a worthy subject for this evening's divertisement--not so much the man, although he is of considerable interest, but the reasons for his spectacular oblivion.

Charles Eucharist de Medicis Sajous, M.D., Sc.D., L.L.D., was born at sea under the American Flag, near the coast of France on December 13, 1852, the son of Count Charles Roustan de Medicis-Joigne, the head of a prominent Florentine family of French-Flemish origin. The name Sajous was acquired from his stepfather, James Sajous, who presumably married his mother after the death of the Count. The young Sajous was privately educated in France, began his medical studies at the University of California, and graduated with an M.D. degree from Jefferson Medical College in Philadelphia at the age of 25. Two years later, he was appointed Professor of Anatomy and of Physiology at the Wagner Institute and then successively served as a clinical lecturer in Laryngology at Jefferson Medical College, as Dean and Professor of Laryngology at the Medico-Chirurgical College of Philadelphia, as Professor of Therapeutics at Temple, and as Professor of Applied Endocrinology at the University of Pennsylvania Graduate School of Medicine, where he occupied the first chair in Endocrinology in the history of medicine, a post which he held until his death in 1929 at the age of 76.

In 1888, Sajous undertook the task of editing what he named "The Annual of the Universal Medical Sciences", which was to be an encyclopedia of the entire medical literature.

The title alone provides considerable insight to its author. Five volumes of this monumental work appeared every year until 1896; forty-five volumes in all, of which 500,000 were sold. This was followed by his "Analytical Encyclopedia of Practical Medicine", in eight volumes, designed especially for the general practitioner. Over 240,000 volumes of this work were also sold.

In 1892, Sajous dropped his practice and institutional appointments in Philadelphia and returned to France for a period of study with none other than Brown-Séquard. Nine years later, he published the work entitled, "The Internal Secretions and the Principles of Medicine", in two volumes and 1,873 pages, which went through nine editions, the last in 1922. For these grandiose labors he received more honors than one can easily recount. Dr. Sajous was with little question one of the leading figures in the medicine of his time (1,2,3,4).

His obituary in American Medicine (1) began with the statement that "The name of Dr. Charles E. de M. Sajous will go down to posterity as one of those pioneers to whom medicine owes each forward stride it makes". Clearly this was not to be. Unhappily, our first president, so eminent in his own day, not so many years ago, and despite his prodigiously voluminous writings on the subject, cannot be remembered for a single original contribution to Endocrinology. The reason for this sad conclusion is simple: he was blind to the ways

of science. He even chose to engage it in mortal combat, a battle which he was bound to lose.

Sajous came onto the endocrinological scene during one of its most seminal periods. Addison had published his epoch-making findings in 1855 (5) and in the following year, Brown-Séquard, one of Sajous' idols, reported that the extirpation of the adrenal glands in several species of experimental animals invariably led to their demise. Although it took some years to establish, and not without turbulence, that the fatal consequences of adrenalectomy were indeed due to the removal of the glands rather than to the attendant surgical trauma, it eventually became a matter of general agreement that the adrenal glands were essential for life. In 1894 Oliver and Schäfer (6) discovered the spectacular, hypertensive effects of adrenal extracts and, quite pardonably, arrived at the incorrect conclusion that adrenalin, secreted by the medulla, maintains the normal blood pressure by a tonic action on the heart and blood vessels (the so-called tonus theory of adrenal function) and that the loss of this function easily accounts for the characteristic symptoms of Addison's disease and for the sequelae of adrenalectomy in experimental animals (7).

Predictably, this new intelligence led to the widely held belief that all diseases which had one or more of the symptoms resembling those of Addison's disease, that is to say, asthenia, hypotension, hypothermia, emaciation,

rapid breathing, cyanosis, weak pulse, vomiting, diarrhea, syncope, and death, were the consequence of varying degrees of adrenal malfunction, and quite curable by the judicious and timely administration of a little adrenalin. Not many human afflictions escape this array of symptoms, but those maladies which did, and could not be readily explained by adrenal insufficiency, were ascribed to the hypersecretion of the adrenal glands.

It was Dr. Sajous' misfortune that he enthusiastically embraced this unifying theory of disease. Being a passionate encyclopedist of medicine, he could endlessly cite from the physiological, pathological, and clinical literature in support of this view thus cloaking it in redoubtable scholastic impregnability.

If that were not sufficient a contribution, Dr. Sajous proposed, and defended to his death, a theory of the mode and mechanism of action of the adrenal principle. It is too exotic and too convoluted to summarize adequately in this time and place, but suffice it to say, that recognizing respiration as a central bodily function, Sajous believed that adrenalin played a critical role in the transport of oxygen by the blood and thus influenced all metabolic processes (8). With time, this view was elaborated to include the adrenal principle as the active portion of all enzymes, and the prime mover of the activities of all cells. Indeed, he described epinephrine as the "dynamic element of life".

Dr. Sajous was chagrined beyond measure that the

physiological community of his time paid no attention whatsoever to his prolific pronouncements. In return, he publicly and repeatedly berated physiologists for their failure to provide satisfactory explanations for any of the bodily functions, to say nothing of disease, whereas he was able to do so without much difficulty.

In 1907, he published a paper entitled, "The Shortcomings of Physiology as the Chief Obstacle to Medical Progress" (9). (It should be remembered that by Physiology, Sajous meant experimental medicine in the broad sense). In this paper, after enumerating the shortcomings of physiologists, Sajous concludes "that we cannot expect from physiologists the solutions we seek. The reason for this is plain: while their laboratory experiments, their only resource, elucidate certain phases of a question, they are totally inadequate to solve the whole question". He goes on to say that the experience of the clinician, an experience of which the physiologists are bereft, will bring solutions to the problems of medicine, solutions to which the practitioners of science could only contribute peripherally. Dr. Sajous endlessly reiterated this theme in all his papers and all his books.

The medicine based on the tonus theory of adrenal function expanded and flourished and filled volumes, and then shelves of medical libraries around the world. Our own library does not quite know what to do with the voluminous collection of Sajous' untouched works donated by grateful alumni.

But the physiologists bided their time. And then, they demonstrated in rapid succession that: 1) the adrenalin secreted by the adrenal medulla had no influence whatsoever on the maintenance of blood pressure, thus demolishing the tonus theory of Oliver and Schäfer in one blow, and 2) that it was the adrenal cortex and not the adrenal medulla which was essential for life. In fact, the administration of adrenalin to adrenalectomized animals hastened their demise.

Swale Vincent, then the Professor of Physiology at the University of Manitoba, spoke for the physiologists when he wrote in 1917 (in the very first volume of Endocrinology) that the views of some clinical writers notwithstanding, "The fact is that we have not a single physiological observation which throws any light on the pathology of Addison's disease" (10). He asks the question: "Why is the extirpation of the adrenal cortex fatal?" and answers, "We simply do not know".

The gauntlet was thrown and the battle was joined.

A few months later, in the first presidential address before this Society, 60 years ago to the day, Sajous responded to Professor Vincent. "Gentlemen" he said, "it is difficult to conceive how all the work done since Oliver and Schäfer published their first paper on the influence of adrenal extracts on the blood pressure, twenty four years ago, or indeed since Brown-Séquard published his initial dissertation on the adrenals over 60 years ago, can thus have proven futile. My own belief is that such is not the case." He then went on to review all the reports associating a vast variety of clinical conditions with purported adrenal disfunction

including an incredible account of the fatal consequences of grafting dog adrenals into four children! He presents once more, and in extenso, his respiration theory of adrenal function which he had first proposed 15 years earlier. In the process, he dismisses all of the scientific arguments of physiologists to the contrary while developing his own, seemingly metaphysical, explanation of bodily function and disfunction. After some parting shots at the myopia and general incompetence of physiologists, he concludes his presidential address, which must have taken at least two hours to deliver, on the benign and healing note that when all is said and done, the cooperation between physiologists and clinicians will hasten our knowledge of the endocrine glands (11).

But the physiologists were not to be so easily mollified. In 1921, Stewart, in a magnificent paper entitled, "Adrenal Insufficiency" (12), reviewed the physiological literature which led to the inescapable conclusion that the consequences of adrenal deprivation could not be assigned to a decline in epinephrine production, and then proceeded to analyze, in language dripping with sarcasm, the clinical views dealing with this subject. He writes that he fails to understand how, even in the case of Addison's disease, the majority of clinical writers "seem still to suppose that it is the loss of epinephrine secretion of the medulla which is the important thing, although experimental physiology affords no basis for such a view". Referring to a communication entitled, "Endocrinopathic Constitutions and Pathology

of War", Stewart says, that "the author speaks of the hypoadrenal constitution as a clinical and pathological entity. On reading this paper and many others by clinical endocrinologists, especially the French and Italians, the physiologist can scarcely escape the feeling that he has broken through into an uncanny fourth dimension of medicine, where the familiar canons and methods of scientific criticism have become foolishness, where fact and hypothesis are habitually confounded and nothing is but what is not." He goes on to sprinkle venom on other clinical deductions as being "scarcely more than the product of an undisciplined imagination". He asks: "in the absence of evidence that fatigue diminishes the output of epinephrine, what is the use of a clinical observer looking at a sick man and saying, 'No doubt he is suffering from capsular exhaustion due to excessive war fatigue or shell shock'?"

Stewart reports that sea sickness has been attributed by one author to hypoadrenalism due to the inhibition of the adrenals by the rolling of a ship while another blames it on hyperadrenalism due to the stimulation of the adrenals by the rolling of a ship. He notes with astonishment that both authors recommend adrenalin as an efficacious treatment.

He concludes that "in the mouths of these authors, hypo- and hyperadrenalism are but words and in science, words which conceal or even distort the facts do not leave a sweet savor".

Sajous rose to the occasion in an address to the Endocrinological Society of the City of New York entitled,

judge whether any given hypothesis is or is not correct?

"Adrenal Insufficiency from the Viewpoint of the Clinician", which was published in Endocrinology in 1922, a year after Stewart's assault (13). But Sajous, while intrepid and undaunted to the end, is clearly on the defensive. He proposes that if Stewart worked in the clinical field his conception of adrenal insufficiency would be different since physiologists never witness hypoadrenemia as a pathological entity in their laboratories. He then proceeds to review, once more, his personal experiences which lead him to conclude that a host of clinical entities, including normal old age, are caused by a reduction in adrenal function. Sajous rejects Stewart's accusation that clinicians still think of Addison's disease as a medullary deficit, treatable with adrenalin. He avers that most clinicians now believe that both the medulla and the cortex are involved in this malady and that "either the fresh gland, a glandular extract, or the dried tissue, all representing the whole gland must be used to expect beneficial results as shown by the personal study of 120 reported cases".

He points out that just because Stewart's animal experiments do not reveal the symptoms of hypoadrenemia, he cannot conclude that this common affliction, recognized by thousands of physicians, does not exist as a clear clinical entity. He does strike a powerful blow by reminding the physiologist that since they profess ignorance of the causes of Addison's disease and since they claim not to understand the function of the adrenal glands, how can they judge whether any given hypothesis is or is not correct?

Then he goes off on his respiration hypothesis once again and with it, attempts to explain a host of diseases including cholera as though the arguments of the physiologists had never been voiced. He states for example: "I have myself observed and studied the majority of these pathological states, and there is no doubt that with the adrenals interpreted as participants in pulmonary and tissue respiration, appropriate organotherapy, adrenalin mainly (using the whole adrenal gland in chronic conditions such as Addison's disease) is a life saving measure often so marked as to suggest undoubted resuscitation." He concludes that while physiology may be useful in some respects, it does not convey the truth when it attempts to analyze pathological phenomena. Further, he warns that for that very reason, Physiology may be dangerous to your health and "may prove costly in human lives--a fact which should inspire great reserve in the presence of therapeutic results attained, even though they disagree with experimental observation which at best cannot but offer a frail foundation for a final judgment."

In a curious volume entitled, "Strength of Religion as Shown by Science", which was published in 1926, Dr. Sajous wrote, concerning the generation of nerve impulses: "A multitude of theories have been vouchsafed, but the only one which has been sustained experimentally so far is one suggested by myself in 1903". What he refers to is his belief that adrenalin is the life force of all cells, including nerve cells.

In the meantime, the physiologists, Stewart among them, were well on the way of preparing the first extracts from the adrenal cortex which were to prolong the lives of experimental animals. Our young science was irrevocably launched while the pronouncements of our first president hurtled into oblivion.

Is there a moral to be drawn from this sad tale other than that one should not tangle with Physiologists? Clearly, there is more than one and I am certain that you will readily discover them all.

Thank you and good night.

## Acknowledgments

I am deeply indebted to Ms. Janet K. Sondecker, Curator of the Historical Collection, Maurice and Laura Falk Library, University of Pittsburgh School of Medicine, for her invaluable assistance.

1. Sajous, Charles Euchariste de Mediciis, Who's Who in American Medicine, 1925, New York, Who's Who Publications, 1925, p. 1290.
2. Sajous, C.E. deM., Obituary, N.Y. Medical Journal 94:1184, 1911.
3. Sajous, Charles Euchariste de Mediciis, Who's Who in American Medicine, 1925, New York, Who's Who Publications, 1925, p. 1290.
4. Addison, T., On the constitutional and local effects of disease of the supra-renal capsules. London, S. Highley, 1855.
5. Oliver, G. and E.A. Schafer, J. Physiol. 16:1, 1894.
6. Oliver, G. and E.A. Schafer, J. Physiol. 18:230, 1895.
7. Sajous, C.E. deM., Endocrinology 9:441, 1926.
8. Sajous, C.E., Gaillard's Southern Medicine (Savannah) 87:44, 1907.
9. Vincent, S., Endocrinology 1:140, 1917.
10. Sajous, C.E. deM., Endocrinology 2:258, 1918.
11. Stewart, G.W., Endocrinology 5:383, 1921.
12. Sajous, C.E. deM., Endocrinology 5:197, 1922.

References

1. Dr. Charles E. deM. Sajous (obituary). American Medicine 35:306, 1929.
2. Charles E. deM. Sajous (obituary). Med. Journal and Record 129:591, 1929.
3. Our new chief. (Editorial) N.Y. Medical Journal 94:1184, 1911.
4. Sajous, Charles Euchariste de Medicis, Who's Who in American Medicine, 1925, New York, Who's Who Publications, 1925, p. 1290.
5. Addison, T., On the constitutional and local effects of disease of the supra-renal capsules. London, S. Highley, 1855.
6. Oliver, G. and E.A. Schafer, J. Physiol. 16:i, 1894.
7. Oliver, G. and E.A. Schafer, J. Physiol. 18:230, 1895.
8. Sajous, C.E. deM., Endocrinology 9:441, 1925.
9. Sajous, C.E., Gaillard's Southern Medicine (Savannah) 87:44, 1907.
10. Vincent, S., Endocrinology 1:140, 1917.
11. Sajous, C.E. deM., Endocrinology 2:258, 1918.
12. Stewart, G.N., Endocrinology 5:283, 1921.
13. Sajous, C.E. deM., Endocrinology 6:197, 1922.

E. Knobil

Department of Physiology

University of Pittsburgh School of Medicine

Pittsburgh, Pennsylvania 15261