A forgotten chapter in the history of the renal circulation: the Josep Trueta and Homer Smith intellectual conflict

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Submitted 19 February 2015; accepted in final form 11 May 2015

Epstein M, Eknoyan G. A forgotten chapter in the history of the renal circulation: the Josep Trueta and Homer Smith intellectual conflict. Am J Physiol Renal Physiol 309: F90–F97, 2015. First published May 20, 2015; doi:10.1152/ajprenal.00075.2015.—This article reviews the pioneering and visionary contributions of the Catalan surgeon Josep Trueta (1897–1977) to the changes in renal circulation that contribute to the pathogenesis of acute renal failure (ARF). An erudite scientist with eclectic interests in physiology, orthopedics, politics, and medical history, Trueta’s initial involvement in wound healing as a trauma surgeon during the Spanish Civil War and the London Blitz is what prompted him to postulate that a trauma-induced “neural effect” on the renal vasculature, with resultant renal arterial constriction could cause ARF. To test his hypothesis, Trueta assembled an experienced radiologist, a renowned physiologist, and a renal pathologist to study ARF in Oxford. They investigated the renal circulation of rabbits in response to diverse traumatic conditions by injecting a radio-opaque substance, using cine-radiography to visualize the flow of blood through the renal vasculature. Trueta’s suggestion of renal cortical ischemia and diversion of blood to the less resistant medullary circulation (Trueta shunt) was criticized by Homer Smith and coworkers. In contrast to Homer Smith’s data, which were derived from clearance studies and renal arteriovenous oxygen, Trueta used the diametrical opposite method of “direct” observation of the renal circulation. Their differing methodologies, direct visualization of the renal circulation as opposed to inferred computations from clearance studies, accounts for some of their conflicting theories. Nevertheless, the proposal of disparate renal flow compartments focused attention on intrarenal hemodynamics. Trueta’s focus on renal cortical ischemia was ultimately validated by the studies of Barger in the dog and Hollenberg and Epstein in human subjects.

Josep Trueta; Homer Smith; acute renal failure; renal circulation; rhabdomyolysis

THE TURBULENT TIMES preceding, between, and after the two world wars of the past century was the period in which medicine began its final metamorphosis from a principally conjectural practical profession that it had been previously to the scientific discipline it has become. Actually, erosion of the scholastic edifice of dogmatic medical knowledge, based primarily on the personal experience of past healers, began with the Scientific Revolution, when the basic sciences emerged and then matured into the laboratory and experimental medicine of the 19th century but evolved principally independently of the clinical practice of medicine. It was the introduction of the quantitative experimental methods of the basic sciences into clinical medicine in the 20th century that propelled the transformation of the empirical practice of medicine into a scientific discipline driven by testable hypotheses that lend themselves to quantification and experimental verification. Although several factors contributed to this transformation, the principal determinants of its success were the transmission (books, journals, electronics), scientification (expanding clinical research enterprise), and mathematization (precision of measurements and statistical validation) of medical knowledge. As a result, certainty entered clinical medicine and ultimately changed the conjectural art of medical practice into the disciplined science founded on clinical investigation that characterizes the medicine of today (19, 44).

It is ironic that it was in the midst of the upheavals of warring nations that the sciences in general and medicine in particular underwent such dramatic advances, seemingly oblivious to their perilous environment. To a great extent, what catalyzed this transformation was the goal-directed targeted research of the war effort that fostered the multidisciplinary investigation of disease states and clinical disorders by applying the tools and methodology of the basic sciences. In essence a change guided by the application of the scientific methods developed for investigating the normal in the basic sciences to the study and management of the abnormalities encountered in clinical medicine (42, 43). This novel approach to biomedical studies characterized by blending bench research into clinical
practice was translational research at its best. The positive results of this integrative process on medical progress during the First World War was qualified as no less than that of “the birth of new medicine” by Clifford Allbutt (1836–1925) in his presidential address to the British Medical Association in 1919 (1). It was actually during the Second World War (WWII) that this interface would prove most productive, and thanks to visionary leaders, such as Vannevar Bush (1890–1944) and A. N. Richards (1876–1966), it led to the post-WWII acceptance of scientific research as a national asset deserving federal support of independent scientific investigation. This was fundamental in the development of academic departments of clinical investigation, in which the laboratories and methods of physiology and chemistry were appropriated and integrated into clinical departments and in the process transformed the art of medicine into a rigorous science (8, 16, 37).

It was during these tempestuous and drastically transformative times that the functions of the kidney were defined, its diseases identified, and its pivotal role in homeostasis established (1, 9). Until then, the kidney was considered a tubular secretory organ that was an adjunct to the gastrointestinal tract in its vital process of nutrition. The kidneys continued to be viewed as secretory organs long after Marcello Malpighi (1628–1694) had described the tiny globular glands that formed his eponymous “corpuscles” and implied their connection to the “canaliculi” and tubules described earlier by Lorenzo Bellini (1643–1704) in the 17th century (34). This notion of the kidney as a secretory gland continued well after William Bowman (1813–1892) demonstrated the actual continuity of Malpighi’s corpuscle with the tubule in 1842 and shortly thereafter when Carl Ludwig (1816–1892) argued convincingly for glomerular capillary ultrafiltration. Debate on the role of glomerular filtration and of tubular function raged in the decades that followed, while the kidney continued to be considered a secretory glandular organ. Indeed, even when the accrued evidence on urine formation was critically analyzed in 1917 by Arthur Cushny (1866–1926) as consisting of glomerular filtration followed by tubular reabsorption, to which he added that of selective tubular secretion in the 1926 second edition of his book, he termed both editions of his book “The Secretion of the Urine” (18, 45).

It was in the interval between the two World Wars that the functions of the glomerulus and that of the different segments of the tubule would begin to be elucidated. Also, as new information was generated after WWII, the concept of the kidney underwent its revolutionary metamorphosis from a mere “excretory servant” to nutrition to that of a “master chemist,” essential to the very processes of life (13, 44, 45). During the early stages of this transformation, studies of the kidney were undertaken by an increasing number of physiologists, pathologists, internists, and surgeons with widely varied interests, in addition to the kidney, none of whom would have considered themselves nephrologists (37). It was the conceptual and technical advances achieved during and around the years after WWII that were to change this fragmented course of renal studies. To a great extent, this was a product of the targeted research of the war effort on shock, hemorrhage, blood replacement, and crush injury, which proved critical to the identification of acute renal failure (ARF) and the development of its treatment (hemodialysis) (11, 12, 35). Both targeted renal research and the worldwide spread of dialysis were to prove instrumental in the emergence of nephrology in the post-WWII period. Essentially, it was in the 1950s that the seeds of nephrology were planted, nurtured, and matured into the discipline it has become. The revolutionary transformation of medicine presented so far as a product of its times was ultimately shaped by the work of the gifted investigators who guided these changes. The list of these individuals is beyond the scope of this article, which is an attempt to reconstruct the intellectual encounter of two of the most erudite and talented investigators of the period. The first is Homer Smith (1895–1962), a marine physiologist who integrated experimental renal physiology into the study of the kidney in health and disease and went on to become one of the founders of modern nephrology (15). The other, Josep Trueta (1897–1977), was a talented surgeon who honed a multidisciplinary experimental approach to study the changes in renal circulation that promote the pathogenesis of ARF and went on to become one of the founders of modern orthopedics (49, 56). Their meeting ground was a product of the directed WWII effort to study diseases of high mortality: traumatic shock, the crush syndrome, and the consequent development of acute renal failure. Whereas the contributions of Homer Smith to the subject have been widely reported and duly recognized, regrettably those of Josep Trueta have gone unnoticed and consequently constitute the focus of this article.

Trueta: The Man and the Scientist

Josep Trueta (Fig. 1) was a scientifically minded Catalan surgeon with eclectic interests in physiology, orthopedics, politics, and medical history, who for a transient period in his career achieved worldwide renown as a renal physiologist (54, 56). His early contributions to wound care saved the lives of thousands. He was one of the first to recognize the importance of blood supply to bone health and healing. As an innovative student of renal physiology, his prescient notions and studies of renal blood flow left an indelible mark on our understanding of renal hemodynamics and kidney function.

Trueta was born in Barcelona in 1897 into a family with a long tradition of medical and military service. He studied medicine at the University of Barcelona and graduated in 1921. In 1929, he was appointed surgeon to the Caja de Provision y Socorro, which treated more than 40,000 industrial accident cases a year. It is then that he began his earliest research in osteomyelitis and wound care based on the principles of tissue physiology and blood supply. His innovative research culminated in what came to be known as the “Trueta method” for the management of traumatic bone injuries. It consisted of prompt surgical debridement, cleaning, drainage, and immobilization of the injured site with plaster. In what could be considered a turn of fate, he was promoted to chief surgeon and professor of surgery at the University of Barcelona just about the time of the outbreak of the Spanish Civil War (1936–1939). He stayed in Barcelona throughout the war, applying and refining his method in the treatment of war injuries sustained by the victims of the heavy aerial bombing of Franco’s air force (17, 56).

As Franco’s Nacionales descended on Barcelona in 1939, Trueta, along with many Republicans on the losing side of the war, fled Barcelona across the Pyrenees to Perpignan, France. By then, his work had already attracted the attention of the leadership of the British war preparation effort, which already
had established contact with him when an otolaryngologist, Josephine Collier (1897–1987), and a war surgeon, Ernest M. Cornwell (1886–1971), had visited him in Barcelona in 1938. Josephine Collier contacted him again in Perpignan and convinced him to go to the United Kingdom (56). By then, he had already published his classic papers on the treatment of war fractures by the closed method and on the organization of hospital services for casualties due to bombing of cities, and his reputation had preceded him to England (49, 50).

Arriving in London, just before the outbreak of WWII, Trueta was appointed advisor to the Health Ministry and made several presentations of his experiences in the Spanish Civil War to British and Allied military medical personnel. It was in the course of one of these presentations at the Royal Society of Medicine that a gentleman in the audience introduced himself to research is eloquently expressed in the conclusion of his book, The Spirit of Catalonia, a learned geopolitical recounting of the history of Catalonia from its origins in northern Iberia, highlighting the cultural contributions of Catalans to world civilizations. He dedicated the book to his Catalan friend-in-exile, the preeminent cellist Pablo Casals (1876–1973). In 2005, to honor Trueta’s memory, members of his family reproduced on the Web the original book published by Oxford University Press in 1946 (52).

Shortly after his arrival in Oxford, Trueta started working in the laboratories of Howard Florey (1898–1968) in the William Dunn School of Pathology. This afforded him the opportunity to work with and learn from a group of renowned investigators including Ernst B. Chain (1906–1979), Florey’s chief biochemist. Florey and Chain were to share the 1945 Nobel Prize in Physiology or Medicine with Alexander Fleming for the discovery of penicillin (Fig. 2). As fate would have it, Trueta assisted Chain in injecting the experimental animals during the initial studies leading to the discovery of penicillin (56).

Eventually, Trueta published some 187 papers, half of which were original research; 12 of his research papers, published between 1942 and 1955, were on the kidney. His commitment to research is eloquently expressed in the conclusion of his Preface to the Studies of the Renal Circulation (52), where he quotes the medieval Catalan poet and philosopher Auzià: “Whatever end man aims at in the world is not the final end, for it gives not man full happiness. What was an end becomes a new beginning, according to the course that man can understand."

Trueta: The Renal Physiologist

Following his move to Oxford, Trueta embarked upon his studies of organ perfusion. Based on initial studies of the splanchnic circulation done with the experimental pathologist John M. Barnes (1913–1975) and published in 1942, they postulated that the arterial constriction demonstrable in the splanchnic vasculature probably also occurred in the renal circulation, promoting the oliguria of ARF. When asked for his opinion as to the cause of shock and anuria in casualties from air raids, Trueta postulated that it was attributable to a “neural effect” on the renal vasculature, with resultant spasm of the renal circulation, leading to renal failure and anuria (52, 56). To test his hypothesis, Trueta moved to the Nuffield Institute for Medical Research to pursue his studies of the renal circulation in the laboratory of the renowned physiologist Kenneth J. Franklin (1897–1966) with the active collaboration of the well-known radiologist Alfred E. Barclay (1876–1949). They then recruited an expert pathologist, Peter M. Daniel (1910–1991), to join their investigative group. This was multidisciplinary research at its best. They studied the renal circulation of rabbits by the intra-aortic injection of a radio-opaque substance (50% solution of sodium iodide in saline) and used cine-radiography to visualize and record the flow of blood through the renal vasculature. After establishing their methods, they induced shock in rabbits by means of tourniquets applied to the thigh (reflecting the prevailing clinical interest in the crush syndrome), and radiographically documented the consequent changes in the renal circulation. While their principal exper-
ments were done in rabbits, they also studied dogs, cats, rats, and guinea pigs and examined the renal circulatory changes in response to ischemia induced by stimulation of the sciatic and renal nerves or by the injection of *Staphylococcus* toxin, adrenaline, pitressin, and ephedrine. In 1947, they published a book, *Studies of the Renal Circulation*, summarizing the body of their studies (52). They proposed that the kidney had two circulatory beds, a major or cortical circulation and a central or medullary circulation: in other words, a major and minor circulatory system.

Apart from their conceptual contribution to the understanding of the shock kidney, Trueta’s emphasis on the importance of direct visualization of the renal circulation was a pioneering endeavor that launched novel approaches to the study of the renal microcirculation, which have witnessed a dramatic growth of innovative techniques in the recent past (4–6). These include corticotomy of isolated, perfused kidneys (32, 47) and renal microvessels (29), vascular casting of perfused juxtamedullary nephrons (14), and intravital charge-coupled device videomicroscopy (24).

Trueta’s book was so well received that it was heralded in the August 11, 1947, issue of *TIME* as “like Sir Alexander Fleming’s discovery of penicillin” the studies of “Spanish-born Dr. Josep Trueta and four co-workers at Oxford’s Nuffield Institute of Medical Research” of “what crushed legs had to do with the kidneys” showed a “detour of blood circulation from the cortex”, and went on to speculate on how this mechanism “caused by too much nervous excitement” might cause hypertension (2).

Following the publication of the book, Trueta was invited to present his findings throughout the world and asked to write the chapter on the kidney in the 1950 edition of the *Annual Review of Physiology* (54). His insights and familiarity with the renal literature is reflected in his explanation of the dedication of his book, *Studies of the Renal Circulation*, to “William Bowman, who was led through structure to function; Claude Bernard, who became interested in structure through function; and Richard Bright, who was the first to appreciate the altered function and structure of the kidneys in disease” (52).

**The Conflict**

Trueta’s *Studies of the Renal Circulation* was not well received by everyone in the United States, where it was repudiated by some physiologists, notably Homer Smith, whose application of the clearance concept to the study of kidney function in the 1930s had finally provided some analytic grasp of how the kidney actually worked and by then established him as the revered leading authority in renal physiology (15). In a 1950 review based on their own clearance studies and the relevant literature, Smith and his coworkers (33) questioned and critiqued the observations and interpretations of Trueta and his coworkers at Oxford. Accepting the duality of the renal circulation and admitting the possibility of renal circulatory diversion from the cortex to the medulla following ischemic injury in rabbits, Smith and coworkers argued that there was no evidence of appreciable diversion of blood from the cortex to the less resistant medullary circuit in humans or dogs following ischemic injury and that the juxtamedullary glomeruli do not afford the proposed bypass by which blood is diverted from the cortex. The data presented by Smith and his associates were derived from clearance and extraction studies of inulin and PAH and of renal arteriovenous oxygen differences. Essentially, these studies treat the kidney as a black box in which the input (arterial blood) and output (venous blood and urine output) are actually measured but the derived information (clearance and extraction) is calculated. This approach is the diametrical opposite method of direct observation of the renal circulation used by Trueta and his associates. Therein also lies some of the concerns of Homer Smith, the meticulous mathematician and consummate scientist. The entire text of Trueta’s *Studies in Renal Circulation*, while extensively illustrated, contains not a single table, calculated value, or any statistical analysis (52). While unthinkable in today’s literature, in this early pioneering era experi-
mental studies were just transitioning from a prosaic and descriptive format to a much more analytic focused style already adopted and actively promoted by Smith. The available evidence suggests that Trueta was well aware of this and was collecting additional data for that very purpose (Fig. 3) but was deviated from it all by his promotion to the Chair of Orthopedics in Oxford (Fig. 4).

It should be emphasized that Trueta’s book includes normal human kidney injection studies showing a dual renal circulation similar to those demonstrated in rabbits. Importantly, in a presentation to the Royal Faculty of Physicians and Surgeons, Glasgow, UK, on November 9, 1949, Trueta reported his findings on the kidneys removed from two patients who died in shock. Examination after the intra-arterial injection of colloidal silver revealed that “the medullary circulation was found to be exceedingly rich and the distribution of intrarenal blood reversed in its normal proportion” (55). In his landmark book The Kidney, Structure and Function in Health and Disease published in 1951 (45), Smith briefly acknowledges Trueta’s work as having “contributed substantially to our knowledge of the finer circulation in the juxtamedullary region by detailed studies of the injected kidneys in several mammals,” but goes on to devote an entire chapter to reiterate and expand on his objections to Trueta’s proposed shunting of blood.

It is relevant in this regard that Trueta’s studies were duly recognized by another founder of nephrology, Donald D. Van Slyke (1883–1971), famous for introducing quantitative chemistry into medicine. In a footnote to his 1948 report of the experimental studies on the effect of shock on renal ischemia carried out during the war with support of the Committee of Medical Research (57), Van Slyke acknowledges the explanation of renal failure during shock “demonstrated in a series of brilliant experiments...” by Trueta and his associates.

It would be some years before American investigators would rediscover and validate Trueta’s observations using diverse methods to determine the changes in renal hemodynamics and glomerular filtration rate in patients with ARF (20, 26–28, 48). These included PAH clearances and extraction ratios, inulin and thiosulfate clearances, and renal arteriovenous oxygen differences (10), the indocyanine green dilution technique (40, 41), renal interstitial pressure approximated from wedged renal venous pressures (9), and the determination of renal hemodynamics derived from radioactive xenon (133Xe) washout curves (30). In general, these studies documented decreases in renal...
In the late 1960s, studies from the Peter Bent Brigham Hospital and the Department of Physiology at Harvard Medical School provided strong support that preferential renal cortical ischemia constitutes the hemodynamic abnormality that mediates ARF. Clifford Barger (1917–1996) and colleagues adapted a diffusible indicator, radioactive krypton (85Kr), for use in a washout technique to study the kidney and demonstrated the presence and functional significance of separate relatively independent circulatory pathways within the kidney (48).

Subsequently, Rosen, Hollenberg, and Epstein, working in the laboratory of John P. Merrill (1917–1984) at the Peter Bent Brigham Hospital succeeded in applying this methodology, using radioactive xenon (133Xe) to investigate intrarenal circulation in human subjects with ARF of diverse etiology (20, 26–28). The results were correlated with the findings of concomitant selective renal arteriographic studies and the findings at open kidney biopsies. The selective arteriograms consistently failed to opacify and demonstrate fifth-order or intralobular arteries. The xenon washout studies consistently demonstrated the absence of an early rapid component, indicating prevailing renal cortical ischemia. The most direct observations were derived from the open renal biopsies, which were associated with subnormal to absent bleeding when the renal cortex was incised (26). These findings provided strong support to the formulation that preferential diffuse cortical ischemia was present in all patients with ARF.

The Sequel

An early champion of Trueta the Physiologist was John F. Fulton (1899–1960), the Sterling Professor of Physiology at Yale University. He greatly admired the research of Trueta and was a constant supporter, mentor, and booster of his academic career. Commenting on one of Trueta’s key articles on the renal circulation, Fulton sent him a telegram in 1947 reading: “Warm congratulations renal discovery most important disclosure since insulin” (56). Fulton often invited him to Yale to lecture on his studies of renal physiology and writings on medical history. A seminal event of their relationship was...
Fulton’s recommendation of Trueta for the Moseley Chair of Surgery at Harvard, vacated on the death of Elliot Cutler (1888–1947). Trueta was invited to Boston on February 2, 1948, to deliver a series of lectures at the Peter Bent Brigham Hospital, the Massachusetts General Hospital, and the Hotel Beaconsfield in Brookline.

In the end, he was not selected for the Moseley Chair. As detailed in the Search Committee’s notes of their November 5, 1947 meeting, one of the adopted criteria was that of recruiting a young candidate of outstanding accomplishments in a given field of surgery. Trueta was then 50 yr old, and the chair was awarded to the 34-yr-old Francis D. Moore (1913–2001). In a letter dated July 9, 1949, John Fulton explained to Trueta that by the time his nomination was submitted Francis Moore had already “been approached” by the Search Committee (22a).

This minor setback notwithstanding, in June 1949 Trueta was selected as the Nuffield Professor of Orthopedic Surgery at Oxford to succeed his mentor Cathorne Robert Girdelstone. Unfortunately, the appointment meant that he had to abandon his research in renal circulation, and as noted in his autobiography, a colleague wrote him saying, “Not pursuing this research was like a miner discovering a gold mine and leaving it to be exploited by others.”

A Personal Perspective

As a young trainee in the Cardiorenal Laboratory of the Peter Bent Brigham Hospital (now Brigham and Women’s Medical Center) who participated in the final set of studies that validated most of Trueta’s findings in ARF (20, 26–28), one of the coauthors (M. Epstein) was “close to the action.” What follows is his personal perspective of how the story unfolded.

My introduction to the conflict began at the start of my training when I was encouraged to read the classic review on ARF written by my mentor, John P. Merrill (35). In discussing the pathogenesis of ARF, Merrill described the pivotal role of a decrease in renal blood flow and referred to Trueta’s postulate that ascribed the oliguria to a diversion of renal blood flow from the cortex to the medulla through the juxtamedullary glomeruli. While acknowledging that this formulation was “vigorously disputed” by Homer Smith, Merrill referred to the studies of Powers et al. (39) demonstrating a fall in urinary oxygen tension in experimental posttraumatic ARF. Merrill concluded that the observations of Trueta were consistent with his own visual “…findings at autopsy of patients dying of acute renal failure with patchy cortical ischemic lesions and a congested medulla” (35). It was my reading of Merrill’s review article that prompted me to access both Homer Smith’s critical review article (33), and also a copy of Trueta’s book (52), thereby providing me with an exposition to the two opposing theories.

As my fellowship progressed and I participated in our ongoing experimental studies, I was persuaded of the importance of renal cortical ischemia in ARF. The constellation of concomitant xenon washout studies, selective renal arteriograms, and open renal biopsies were compelling (20, 26). I concluded that Trueta’s pioneering studies to directly visualize the renal circulation had correctly foreshadowed the multiple visual techniques that subsequently would elucidate the pivotal role of intrarenal hemodynamics in renal ischemia (20, 26–28, 36). In my excitement, I wrote Trueta a letter about our findings including reprints of the key articles. A month later, in November 1970, Trueta responded with a warm congratulatory letter of appreciation (Fig. 4). In the letter he mentions how his research had “roused the antagonism of Homer Smith” who relied exclusively on clearance studies, and in a bittersweet comment how his promotion to the “Chair of Orthopaedics in Oxford” deviated from his path in renal studies.

A final perspective on how my current investigative interest in renal denervation and resistant hypertension links with Trueta’s initial formulations and hypotheses. While the present review focuses primarily on intrarenal hemodynamics and diverse investigative approaches to delineate these changes, we must remember that Trueta’s scientific contributions were broader. In his initial publications, Trueta postulated that acute oliguric renal failure was attributable to a “neural effect” on the renal vasculature, with resultant spasm of the renal circulation (3, 52, 56). Trueta’s theme of a pivotal role for renal sympathetic activation as a determinant of renal hemodynamic alterations has been a recurrent theme in my investigative career. My earlier study of the pathogenesis of the hepatorenal syndrome attributed many of the systemic and renal hemodynamic alterations to elevated sympathetic tone (20, 21). More recently, I have participated in the recent renaissance of investigative interest in renal sympathetic activity in the context of patients with resistant hypertension (22).

So over my extended career in academic medicine, my clinical investigative interests have been linked repeatedly with Josep Trueta’s innovative and visionary proposals relating to both the renal circulation and also to renal sympathetic activation.

Final Outcome

In the context of Trueta having been considered a leading candidate for appointment to the Moseley Chair of Surgery at the Peter Bent Brigham Hospital, it is ironic that the ultimate validation of his postulate of renal cortical ischemia in ARF was validated by renal hemodynamic investigations conducted at the very same institution where he had been considered for the Moseley Chair of Surgery. The irony is further compounded by the fact that it was funding from a research grant from the successful appointee to the Moseley Chair of Surgery, Francis Moore, which helped fund the $35Xe washout studies conducted at the Peter Bent Brigham by Hollenberg and Epstein (26).

Trueta’s perseverance in his research despite withering criticism informs importantly about how scientists should cope with controversial crosscurrents of scientific intercourse. As one of Trueta’s heroes, Claude Bernard, famously opined, “When the observed evidence is opposed to a theory prevailing at the moment, one must accept the data and give up the theory, even when it is supported by famous names and widely accepted (7)."

ACKNOWLEDGMENTS

We acknowledge the invaluable support of Eugènia Serra, Director, and Lourdes Martínez González of the Servei d’Accés i Obtenció de Documents of the Biblioteca de Catalunya in providing access to the original archives, correspondence, and laboratory notes of Josep Trueta. We thank Amèlia Trueta Llacuna for her gracious hospitality and for relating details of her father’s academic career and research in Barcelona and Oxford. We thank Catherine Pate, the Brigham and Women’s Hospital Archivist, for providing access to the correspondence related to Josep Trueta and the deliberation of the Moseley Chair of Surgery Selection Committee. We acknowledge the excellent editorial
support of Kim Jaimes in the preparation of the manuscript. We also acknowledge the assistance of Christine Kitler for accessing many of the articles, and the expert assistance of Larry Gilstad of the Miami VA Medical Center for scanning the archival material and reproducing two of them for inclusion in this manuscript.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: M.E. provided conception and design of research; M.E. analyzed data; M.E. and G.E. prepared figures; M.E. and G.E. drafted the approved final version of manuscript.

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