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A personal recollection: 60 years in thermoregulation

This subjective essay is a personal reminiscence of my 60 y as a thermophysiologist. I recall the academic environment that I entered in the mid-50s, review our knowledge of thermoregulatory mechanisms then, and note the research that exploded in the 60s and continued through the 90s to bring us to our present state of sophistication. I conclude by mentioning some new research that may signal the future of this field.

I would like to begin by thanking Dr. Andrej A. Romanovsky, editor-in-chief of this Journal, for inviting me to write a Legacy Article on any topic of my choice. Since I have been preoccupied lately with writing and editing the global history of thermophysiology[1] for the American Physiological Society (APS), my mind has been full of reminiscences about the people I have known and the studies that have animated me over the 6o years since I entered the field. I thought it might be interesting to share some of my memories with my older (in both senses of the word) and my younger colleagues who may not be fully familiar with our past. I shall try herein to briefly review that past, reflect on the present, and attempt a preview of the future, strictly from my personal perspective. Please forgive me in advance, therefore, for my unabashed enthusiasm on the one hand and my critical biases on the other.

The past

When I started graduate school at the State University of Iowa in January 1954, I knew nothing about thermal physiology. But I learnt about it very quickly: literally upon my arrival, the department chairman, Dr. Harry M. Hines, assigned me to one of his faculty who had an opening for a new student. He was Dr. Steven M. Horvath, and I was very soon regulating my own body temperature – as a subject in the cold room! Indeed, Dr. Horvath was well engaged in temperature regulation research, a field that was then quite active and popular, and growing more so every year. Most of its practitioners were, like Dr. Horvath himself, veterans of the military laboratories that had been created during WWII to conduct intensive research on how to enable combatants to cope successfully with the harsh environments that they were expected to encounter in their campaigns. Indeed, they represented virtually every field of biomedicine, demonstrating the integrative nature of the subject matter. A number of them, moreover, again like my mentor, had had prior experience in environmental physiology, having studied before the war with the pioneers of the field, such as D. Bruce Dill and John Talbott at the Harvard Fatigue Laboratory, Eugene DuBois at the Russell Sage Institute, Charles Winslow, Lovic Herrington and Pharo Gagge at the John B. Pierce Laboratory, Edward Adolph at Rochester, Francis Benedict and Thorpe Carpenter at the Carnegie Nutrition Laboratory, Henry Bazett at Pennsylvania, to name but the best known. For that matter, their teachers, the scientific grandfathers of my generation, had likewise been heavily engaged in the war effort, serving in uniform in the armed forces or as civilian researchers in the military laboratories. Thus, driven by the emergency of the war, they had variously analyzed in great detail the body's physiological and biochemical responses to ambient heat and cold, assessed human physical and mental capacities in all kinds of climates, investigated the influence of different clothing fabrics, diets, and devices on the overall performance, endurance, sense of comfort and, of course, combat efficiency of soldiers (see, for example, Folk[2]). As a result, great progress had been made in clarifying the regulation of body temperature and its adjustments under a wide variety of environmental conditions (see the classic "Physiology of Heat Regulation and the Science of Clothing"[3]). Nevertheless, these studies provided only the framework of the basic physiology and pathophysiology of temperature regulation, such that there remained many unanswered questions and a genuine interest in addressing them. Unfortunately, the Fatigue Laboratory and the Carnegie were disbanded shortly after the war, depriving their past members, when they were demobilized, of their former workplace. Fortunately, however, new government funding of mass college education (the G.I. Bill was signed by FDR in 1944, his last act under the New Deal) and of health-related research and graduate training (the NIH-wide grants program and the NSF were established in 1946 and 1950, respectively) became available so that old and new researchers were able to move into newly created academic positions, establish their own laboratories, and recruit students. And so, by the time I graduated in 1957, this expansion was well in progress. The masters were again busily working in their old laboratories and their pupils, my generation's scientific fathers, had grown new ones, e.g., Ancel Keyes at Minnesota, Sid Robinson at Indiana, R. E. Johnson at Illinois, Steven Horvath and Ed Folk at Iowa. Others had been recruited by military labs that were continuing in service, e.g., the Army Medical Research Laboratory at Ft. Knox, KY (Allen Keller and George Clark), the Quartermaster's Corps Climatic Research Laboratory at Natick, MA (Harwood Belding), the Chemical Corps Medical Laboratory at Edgewood Arsenal, in Edgewood, MD (Bruce Dill). All these scientists, by the way, young and old, were eminently accessible and friendly, and I had the good fortune of meeting them all early on, admittedly thanks then to the close relationship that Horvath had with them. I was thus plunging in 1957 into a caldron of activity in this country and joined others like me. Some of them were a little older than I because they were returning servicemen who had taken early advantage of the G.I. Bill's education benefits and had graduated 2 to 5 y earlier.

A similar kind of scientific re-awakening was then also taking place all around the world. Physiologists who had conducted thermoregulation research before the war and had, like their American colleagues, been involved in their own countries' wartime efforts, were, from the early 50s onward, resuming their previous activities; new, younger scientists were emerging too. For instance, in Germany, Rudolph Thauer, who had become chair of the department of physiology at Phillips Universitat in Giessen and director of the newly founded Max Planck Institut-Kerkchoff Institut in nearby Bad Nauheim, was recruiting recent medical graduates, among them a young Eckhart Simon and a slightly older Werner Rautenberg, to launch an active exploration of extracerebral thermosensors. And in nearby Marburg, Herbert Hensel was the new chair of the department of physiology at Phillips Universitat, conducting novel neuroelectrophysiological research on peripheral thermoreception while his recently arrived associate, Kurt Bruck, soon to follow Thauer as the chair of physiology in Giessen, was beginning work on the role of brown fat in the nonshivering thermogenic response of neonates to cold. They and a few other senior thermal physiologists, e.g., Juergen Aschoff, were attracting young clinicians to the field and growing them into productive scientists. Similar developments were occurring in other countries, led by their own pioneers, e.g., Joseph Chatonnet in France, Szilard Donhoffer in Hungary, Yas Kuno in Japan, Cyril Wyndham in South Africa, Sir George Pickering in the UK, and Alan Burton and Jan Snellen in Canada. I never met Kuno and Wyndham personally, but knew the others and their students, my contemporaries, early in my career. Unfortunately, their early work was not well known because it was published in their native language in their own national journals and therefore not recognized by their English-speaking counterparts. This handicap was fortunately removed in the mid-60s when most foreign journals began to publish in English as well.

With so many active workers, progress was accelerating. In the US, the *Journal of Applied Physiology* had begun publication in 1948 and, from the mid-60s forward, had become the preferred outlet for thermophysiological papers under the section editorship of James D. Hardy; but other journals were equally interested in publishing original research articles on this subject such that one had many different choices in which to publish. Meetings, symposia and special conferences on one topic or another of thermal physiology occurred frequently and were well attended. The APS met twice yearly then, in the spring usually in Atlantic City, NJ, together with other societies under the Federation of American Societies for Experimental Biology (FASEB)'s umbrella, and again in the fall by itself on a university campus. Younger members and especially students car-pooled to these meetings because flying was too expensive and trains took too long over circuitous routes. The on-campus meetings were often the more enjoyable for their smaller size and more pleasant venue, and the greater ease of mixing, networking and socializing with other physiologists of all stripes. There were multiple sessions on temperature regulation at every meeting, and because there were so many presentations, some of them novel and impactful, discussions were often vigorous and exciting. Indeed, because research in all the subfields of physiology was centered then on physiological regulation, workers in one field regularly attended sessions in other fields, and discussions among colleagues from the different subfields were possible and understandable by all as the same vocabulary was used even when talking about different systems. It was a way to stay abreast of developments in the other fields and to learn from them. The *American Journal of Physiology* was published as a single volume then, encompassing all the fields; sectionalization was not yet a thought. How doable is that today?! The fall meetings were also the best occasions to meet our scientific grandfathers who, despite their legendary status, were, as I already suggested, unassuming, completely approachable, not the least bit arrogant or impatient. It is noteworthy that the popularity and reputation of thermophysiologists were such then that several of these leaders became presidents of the APS (Bazett [1950], Dill [1950–1], Adolph [1953–4], Burton [1956–7], Carlson [1968–9], Horwitz [2002–3]). A section of the APS *Handbook of Physiology* series dedicated to environmental physiology (sec. Four) was published in 1964 under the co-editorship of Dill, Adolph and Wilber and updated in 1996 under Mel Fregly's and my co-editorships.

The first scientific meeting that I ever attended was the 1954 fall meeting at Tufts University, in Boston, MA; I did not yet have a paper to present. An event that particularly impressed me occurred during the 1959 spring meeting in Chicago, IL. The "Thermoregulation Group," the predecessor of today's Environmental and Exercise Physiology (EEP) Section of the APS, had recently been organized by James Hardy, then still at the Sage. Ted Hammel, one of his associates there, had presented earlier during the week his finding that cooling of the hypothalamus of dogs held in a warm environment could initiate shivering. This was strongly challenged by Theodor Benzinger, then at the Naval Medical Research Institute in Bethesda, MD, who believed that only cooling of the skin could cause shivering. For that matter, Hardy and Benzinger had been in disagreement over a number of fundamental concepts for some time. A vigorous, at times acrimonious debate ensued between the 2 after dinner in the German restaurant where we met. No one intervened. It left us all rather awed. The two never addressed each other directly again, I believe.

Working conditions were pleasant in those early days, and a career in scientific research was a practicable option, even an appealing one. Grant applications were easy to write and funding approvals were seldom an issue; the cut-off level was, I think, at around 35%. There were practically no regulations, university or otherwise, limiting one's academic freedom. One generally hired one's own technicians, chose and purchased one's own instruments and supplies, and ordered and cared for one's own rodents (large animals were housed in a vivarium managed by a separate staff). A mechanic in the departmental shop built whatever one designed, and one wired one's own electronic gear. One analyzed one's data statistically with a noisy calculator and hand-drew one's own figures. One generally also selected one's own pre- and post-doctoral students, albeit that post-doctoral training was not yet a requisite for later employment. Indeed, most recent graduates joined departments as junior faculty and were assigned the bulk of the departmental teaching in order to free time for the more senior people to conduct their research! The pressure to get grants and publish or perish was still in its infancy. (In my own case, the draft being in effect when I graduated and I, having been deferred from serving all the previous years to continue studying, was immediately conscripted and assigned to the Army's Medical Research Laboratory at Ft. Knox, KY. I was, however, a NIH postdoctoral fellow thereafter, first at the Institute of Andean Research in Peru and then at the University of Oxford in the UK. I befriended then many of my international colleagues.)

Thus, when I graduated in 1957, we had a pretty thorough knowledge of the thermoeffector responses of mammals to dry and wet heat and cold, at rest and during physical and mental work, in air and in water, during dehydration and hypohydration, indeed under a wide variety of conditions. Field studies of unacculturated populations in Africa and Australia had recently been conducted and provided new information on the nature of adaptive responses to thermal stress. We also had a good understanding of the biophysics of heat exchange and of the substrates underlying metabolic heat production; calorimetry was an important tool in elucidating these functions. The phenomena of heat illnesses, cold injuries, and hyper- and hypothermia were known, but the underlying processes were not. We knew that fever was induced not by invading pathogenic bacteria, but by an endogenous pyrogenic protein elaborated and released by leucocytes activated by these pathogens[4]; but we knew very little about this factor's properties and its site and mode of action. For that matter, the function of fever was itself unclear. Lesion and electrical stimulation studies had localized the body's thermostat to the hypothalamus, but its incoming and outgoing connections were vague. It was viewed as having both control and sensory functions differentially distributed between a heat loss center in the preoptic-anterior hypothalamus and a heat-producing and -conserving center in the caudal-lateral hypothalamus. Thermosensitive endings in the skin were known, but not yet characterized, and thermosensitive neurons in the CNS were conjectured, but not yet demonstrated such that there was debate as to whether the temperature of the blood perfusing these centers or signals from peripheral thermoreceptors was driving thermoregulatory responses. The neural circuits within the brain were mysterious. Some neurotransmitter substances were known to exist in the hypothalamus, but their thermoregulatory functions were unknown. The thyroid and adrenals were believed to play roles in heat production due to the already demonstrated calorigenic actions of their secretions, but the details were vague. The sympathetics were known to constitute the efferent pathway to cutaneous vessels and sweat glands, but the pathway to shivering muscles was unknown. Nonshivering thermogenesis had been observed in rats and was thought to be a part of the process of cold "acclimatization," but nothing more was known about it. The equipment and techniques to explore thermoregulatory mechanisms were still relatively unsophisticated, but the investigators were excited and enthusiastic. It was to be expected, therefore, that great progress would be made apace, and indeed it was explosive from the early 60s forward.

The present

Thus today, thanks to the rational analyses of skillful investigators and the development of innovative analytical and instrumental technologies, manifold classes of diffusible messengers have been identified that variously mediate thermoregulatory responses both in health and disease, with potential impact on therapeutic interventions.[5,6] The endogenous pyrogen of old has evolved into a cascade of interacting mediators that drive multiple-input, multi-centric immunological and neural systems underlying the febrile response.[7] The afferent and efferent neuronal pathways and internal brain circuits that modulate thermoregulation are now much clearer, and multivariate facilitatory and inhibitory processes have been described.[8,9] The existence, distribution and multimodal characteristics of central thermosensitive units are established, and the mechanism of their thermosensitivity is being clarified.[10,11] The discovery of extrahypothalamic thermosensors has led from the original monocentric to the current multiple-input, multiple controller concept of thermoregulation.[12] The distribution and electrophysiological characteristics of cutaneous thermoreceptors have similarly been analyzed,[13] and the molecular mechanisms underlying their responsiveness, i.e., the transient receptor potential (thermoTRP) channel proteins, are increasingly being unraveled.[14] The mechanisms of the thermoregulatory control of skin blood flow and eccrine sweating have been vastly elucidated,[15,16] and the source of nonshivering thermogenesis has been determined to be brown adipose tissue and its operation described.[17,18]

This is obviously a huge abridgement of all that has been accomplished in temperature regulation research over the past 60 y. My apologies to the many distinguished scientists around the globe whose important contributions I have omitted due to the limitations of time and space. Our field has a rich and enduring history, but it is now quite a different discipline from that which I learned as a graduate student in the mid 1950s and, for that matter, practiced for most of my career. Like the other basic medical sciences, physiology is now rooted in molecular biology and molecular genetics that use techniques in which I and many of my contemporaries were not schooled and therefore found initially difficult to access without the necessary background. Thus, speaking for myself, their utility and relevance to the studies I was conducting were not immediately obvious to me. Furthermore, as funding became more competitive, grant application reviewers were demanding expertise in the use of these tools before awarding funds to purchase the necessary equipment and supplies - the proverbial horse and carriage, which comes first!? But it was inevitable that, sooner or later, I and many of my contemporaries would learn and use the new methodologies and, indeed, many of the advances made in my own research were founded over the last 2 decades on these approaches.[7] But one of my concerns now is that, on the contrary, young investigators focused on the new science may be ignorant of the old and consider it an inefficient use of their time to devote attention to the classic literature. The recollection of past research is essential to understanding the field today and to planning its further evolution. For these are different times indeed: many members of my generation here and around the world are gone – retired or, sadly, passed. Challenges imposed by ever more severe funding cuts, by excessive and time-consuming red tape such as regarding human and animal use and biosafety protocols, and by other organizational hindrances have placed undue constraints on current workers' progress and productivity, affecting the number of active researchers and, hence, also that of original articles published in increasingly fewer journals open to this field and of sessions dedicated to thermoregulation research at Experimental Biology meetings and International Union of Physiological Sciences congresses. Moreover, with so much of present-day biomedical research focused on the subcellular and molecular level, most biology undergraduates are now taught the concepts and tools of that approach and are, therefore, more naturally drawn to it rather than to integrative research, reducing the number of recruits into our particular field. Additionally, opportunities in other, different vocations that did not exist 20 y ago, more lucrative and less taxing than ours, have arisen and attracted talented college graduates who earlier might have pursued academic research careers. These conditions have all contributed, in my view, to a waning interest in thermophysiology from about the late 1990s forward in the United States and in some other countries as well.

The future

Have the remarkable advances of the past 60 y answered all the questions? Of course not! And in any case, answers only beget more questions. To wit, 1) nonshivering thermogenesis (NST) in animals in which brown adipose tissue (BAT) is minimally functional, the role of skeletal muscle as its source, and its mediation by sarcolipin are issues under current re-examination.[19] [Please allow me to brag in this regard and cite 2 ignored, 40 year-old papers of mine in which I reported the presence of NST in minipigs and humans when this was deemed implausible.[20,21]. 2) Also of renewed interest following the discovery of cold-induced BAT thermogenesis in humans, its molecular basis and the roles of shivering muscle-derived irisin and of adipocyte-derived fibroblast growth factor 21 in the functional transformation of "beige" adipocytes into brown-like adipocytes.[22,23] [We did not know beige fat then, but to brag a little again, I reported 50 y ago in another ignored paper the conversion of white into brown fat by residence at high altitude[24]]. 3) Consequent to the new data regarding the molecular basis of thermosensation and thermal nociception mentioned earlier, further analysis of the mechanism of sensory transduction in the skin and its potential relevance to pathological conditions is ongoing in several laboratories.[25,26]. 4) The impact of climate change on the adaptive and evolutionary biology, indeed on the very viability of organisms, is an increasing concern driving new research into the alterations in body temperature and associated physiological reactions and genotypic adaptations potentially provoked by long-term exposure to a moderate increase in ambient temperature.[27] 5) In view of the increased morbidity and mortality of, particularly, older people in extremes of environmental temperature, the mechanisms underlying age-related impairments in temperature regulation are under active current investigation.[28] 6) Although much has been learned about the mechanics of the febrile response to endotoxic lipopolysaccharides, studies are lagging regarding the fever produced by other pyrogenic pathogens and, in particular, by live organisms.[29] And 7) clearly much is still to be learned about the wiring and operation of the brain in these contexts.

This brief sampling of ongoing projects is meant to signify that the pioneering spirit of old persists and that thermophysiological research, although seriously challenged, is still robustly alive in this country as well as in some others around the world. Indeed, it may now even appear in different and sometimes unfamiliar guises through the application of innovative technologies and approaches that employ skill sets not usually existent in a single individual and require, therefore, the specialized knowledge of different people working as a team. This seems to be, at present at least, one strategy of scientific research that meets the need for both these practical skills and the continued service of skilled scientists. The strong appeal of other, "easier" or "hotter" fields and the current, low availability of grant money have impeded our progress, it is true, but it is not all gloom and doom.

Congress needs to continue hearing from us, and we must keep up our hope that reason will ultimately return to our policy makers.

To conclude this reminiscence, I retired from active research on October 1, 2008, just as things were getting really bad (the market collapsed on that day!). I miss the excitement of the lab, but I am glad I do not have to compete for funds anymore! I have been extremely fortunate indeed: I worked during the "good times," met exceptional people, and made wonderful friends throughout the world. It has been an amazing journey, and for that I am immensely grateful. To all my colleagues, old and young, I wish continued joy and success in your endeavors.

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