

# Thermal biology in Brazil: a summary of a 100-year legacy

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## The Pioneers

The first studies in the thermoregulation field in Brazil were conducted in the beginning of the 20th century (~1910) in Rio de Janeiro at the laboratory of the siblings Álvaro Ozorio de Almeida (1882–1952), Miguel Ozorio de Almeida (1890–1953) and Branca Ozorio de Almeida (1896–1965) known as “**The Ozorios de Almeida LAB**” (Fig.1). Álvaro Ozorio de Almeida, a professor at the Medical School, installed the laboratory in his home, after being discouraged by the dean from building it at the Medical School. The installation of the laboratory was supported by Cândido Gaffrée, one of the owners of the docks of Santos Port. This

laboratory was the first experimental physiology laboratory in the country and many physiologists consider it the *birthplace* of experimental physiology in Brazil.<sup>1</sup> In Álvaro Ozorio honor, the Brazilian Society of Physiology created a young investigator award with the name of the above-mentioned scientist, in acknowledgment of his contribution for the Brazilian Physiology.

In 1915, the laboratory moved to Dr. Gabriel’s residence (father of Álvaro, Miguel and Branca), where Branca Almeida Fialho joined the group. Branca Almeida Fialho had an important contribution in the implementation of thermal biology studies in different species of wild animals.<sup>2,3</sup> The work of Álvaro Ozorio de Almeida on thermal biology and metabolism became intense between 1913 and 1928. During this period, his group published approximately 20 papers about thermal biology, making him one of the pioneers in studies on microcalorimetry basal metabolism in humans and animals living in tropical climates.<sup>4,5,6</sup>

Indeed, Álvaro Ozorio made an important contribution to the better understanding of human acclimatization to tropical environments. In 1919, he published his findings about the basal metabolism of tropical humans. In this work, he questioned the relationship between basal metabolism rate and body surface area proposed by the Rubner-Richet Law.<sup>7,8</sup> At this time, the current theory about the basal metabolism was that, *independent on the individual’s weight, the basal metabolism should follow Rubner-Richet’s law, which determined that the metabolism of animals with different weights would be proportional to their body surface areas.*

Thus, the basal metabolism of different animal species could be compared independent on differences in their body weights. According to the limits set by Du

Bois and Gephart,<sup>9,10</sup> humans displaying a basal metabolism of approximately 39.7 kcal/m<sup>2</sup>/h with a variation of 10% would be considered normal, and it would be considered pathological when this difference was greater or less than 15%. These limits were calculated based on Lusk table<sup>11</sup> measurements performed on 100 healthy and sick individuals.

Based on this law, it would be possible to compare the rate of thermogenesis of North Americans to that of Brazilians living in a tropical climate. Surprisingly, Álvaro Ozorio de Almeida observed that Brazilian individuals aged between 23 and 40 years old, considered as normal individuals for the Brazilian standards – men born and living in tropical towns, such as Belém do Pará, with an average annual temperature of 25°C (22° – 30°C), and Rio de Janeiro, with an average annual temperature of 23°C (16 – 31°C) – presented a mean value of 30.35 kcal/m<sup>2</sup>/h for basal metabolism.<sup>4,5</sup> The basal metabolism of Brazilians was 24% lower than the average obtained in previous American studies. According to the limits set by Du Bois and Gephart,<sup>10</sup> these individuals would be considered very sick. Based on these results, the authors concluded that healthy inhabitants of warm climates (tropical countries) have a much lower basal metabolism than inhabitants of cold or temperate climates because the former are acclimated to warm environments. According to the authors, acclimatization essentially consists of slow and progressive changes of the basal metabolism, until a fixed and more consistent value is attained that is compatible with the new climate conditions to which the individual is exposed. This process normally requires months of exposition to the new environment before the individual become acclimated.

An important observation made by Álvaro Ozorio de Almeida was that the

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The authors report the history of thermal biology in Brazil over 100 years. This history started with the establishment of the “Ozorios de Almeida laboratory” in 1910 in Rio de Janeiro. Since then, the number of research groups has significantly increased.

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metabolic rate of tropical humans was not consistent with surface law from Rubner-Richet.<sup>7,8</sup> Therefore, considering the minimal metabolism, Álvaro Ozorio de Almeida suggested that metabolic rate was proportional to the normal average metabolism (Mt), depending on the individual lifestyle (nutrition, A; muscle work, m), the climate where he or she lives (difference between the ambient temperature and that of the skin, T-T0), and the skin surface (S). Thus, he proposed the following equation:

$$Mt = f [Tm, A (T - T_0) S].$$

Taking the last term of the equation alone (S), it allows one to establish that the Rubner-Richet surface law would be part of a more complex control system. The author mentioned that the minimal metabolism would depend on the body surface law from Rubner-Richet only when a group of individuals was submitted to controlled nutrition, muscular work and room temperature conditions. In such conditions, the factors Tm, A and T-T0 would become constant, and the result of Mt would depend on S.

However, for the acclimatized human, basal metabolism depends on all of these factors, including the ambient-skin

temperature differences (T-T0), which can have long-term influence and change the rate of the habitual metabolism. Therefore, in this situation, the skin surface would be determinant in the magnitude of acclimation induced by exposure to different ambient temperature.

In 1919, Álvaro Ozorio de Almeida stated that he believed that the law of surface would hardly be discovered by a physiologist working in a tropical climate.<sup>3</sup> “Nous croyons même que la loi de surfaces eût été difficilement découverte par un physiologiste que aurait travaillé dans un climat tropical” (Fig. 1).

Over two decades, this small and sui generis laboratory attracted the attention of distinguished visitors, including Marie Skłodowska Curie and Albert Einstein. However, the laboratory was closed in 1932, when Álvaro started focusing on cancer research. In addition, in 1919, his brother Miguel has taken a neurophysiology research position at the Instituto Oswaldo Cruz (Rio de Janeiro, Brazil).

### The Study of Thermal Biology Arrives in São Paulo

Paulo Enéas Galvão (1902-1977), at the age of 26, was invited to work in the

Physiology Department of the Biological Institute of São Paulo. This institute, established in 1927 is one of the most important and scientifically recognized in Brazil. There, the pharmacologists Mauricio Rocha e Silva (1910-1983), Gaston Rosenfeld (1912-1990) and Wilson Beraldo (1917- 1998) described in 1949 a new peptide called bradykinin. The plasma concentrations of this peptide were increased after exposure to the venom of the viper *Bothrops jararaca*. Later, it was reported that bradykinin was involved in fever induced by lipopolysaccharide (LPS).<sup>12</sup>

At the São Paulo Biological Institute, Galvão (Fig. 2), who worked in the “The Ozorios de Ameid LAB” in Rio de Janeiro until 1928, continued his studies on the basal metabolism in humans and tropical animals, assessing the validity of the well-known “body surface law.” The results of his work on the basal metabolism of Brazilian people living in São Paulo, a city located exactly on the Tropic of Capricorn line, were published in a series of articles in the *Journal of Applied Physiology*.<sup>13,14,15</sup> Galvão reported that the estimation of the basal metabolism using the surface area law was not applicable to humans living in tropical regions. In these



**Figure 1.** Álvaro Ozorio de Almeida and his siblings (L-R): Álvaro Ozorio de Almeida, Branca Almeida Fialho and Miguel Ozorio de Almeida, were 3 important physiologists who built a laboratory at their father’s residence. With permission of Departamento de Arquivo e Documentação da Casa de Oswaldo Cruz/ Fiocruz. Bottom: Sentence written by Álvaro Ozorio de Almeida in the article “Le Métabolisme minimum et le métabolisme basal de l’ homme tropical de race blanche” in 1919 (page 727, paragraph 1, lines 17-19).<sup>4</sup>



**Figure 2.** Left panel: A 1958 photograph of Paulo Enéas Galvão, when he was the counsellor of the National Council for Scientific and Technological Development. (CNPq). Right panel (L-R): Paulo Enéas Galvão and his colleagues, Casaretto and Sebastião Baeta Henriques, in 1965 at the Butantã Institute, São Paulo. Courtesy of Sociedade Brasileira para o progresso da ciência (SBPC).

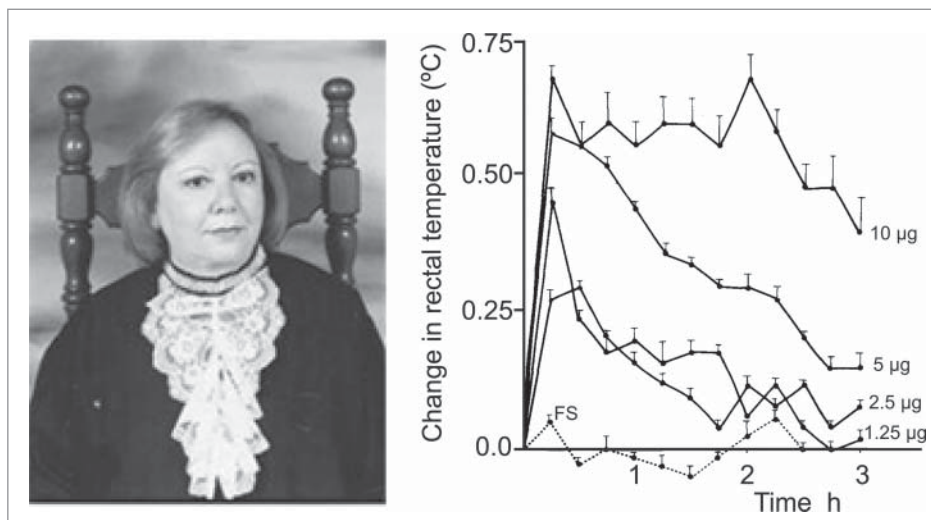
regions, basal metabolism was, in fact, proportional to the metabolic active body weight ( $W$ ) to a certain power, i.e.,  $W^{0.83}$  for lean people,  $W^{0.78}$  for “well-proportioned” people and,  $W^{0.71}$  for obese people, compared to  $W^{0.67}$  calculated for well-proportioned” people from cold climates.<sup>16,17</sup> The basal metabolism of the latter was closely related to their body surface. The difference in heat production in cold and warm climates was thus explained as a *surface effect* seen only in colder climates, in which the skin-to-ambient temperature gradient is increased, thereby facilitating cutaneous dry heat loss.

In 1941, Galvão became the Chair of the Physiology Department of Escola Paulista de Medicina (current Federal University of São Paulo). At this time, he installed the thermal biology and metabolism laboratory together with Jacob Tarasantchi (1927 – 1997), who continued to study the calorimetry of acclimated animals.<sup>18</sup> In 1970, Mauro Antônio Griggio joined their laboratory, focusing his studies on the energy metabolism of animals acclimated to cold.<sup>19</sup> By this time, Jacqueline Luz

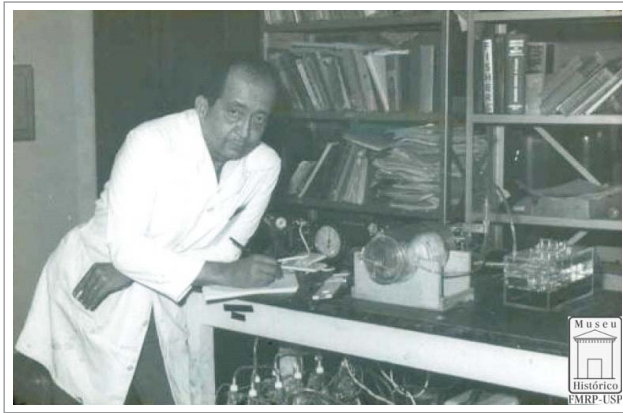
joined their research group, focusing on the energy metabolism and heat production in several other situations, such as food restriction, cold acclimation, diabetes, obesity, pregnancy and fetal programming of body temperature regulation.<sup>20,21</sup>

### From São Paulo to Ribeirão Preto: Thermoregulation, Inflammation and Fever

In 1957, Maurício da Rocha e Silva was invited to teach at Ribeirão Preto Medical School, University of São Paulo.



**Figure 3.** Left panel: Irene Rosemir Pelá at the University of São Paulo when she was elected vice-dean of the Pharmaceutical Sciences School of Ribeirão Preto (1998-2001) Courtesy of school of pharmaceutical sciences of Ribeirão Preto. Right panel: Data from the study of Almeida e Silva<sup>12</sup> showing the changes in rectal temperature following intracerebroventricular injections of 4 doses of bradykinin and vehicle, with permission.



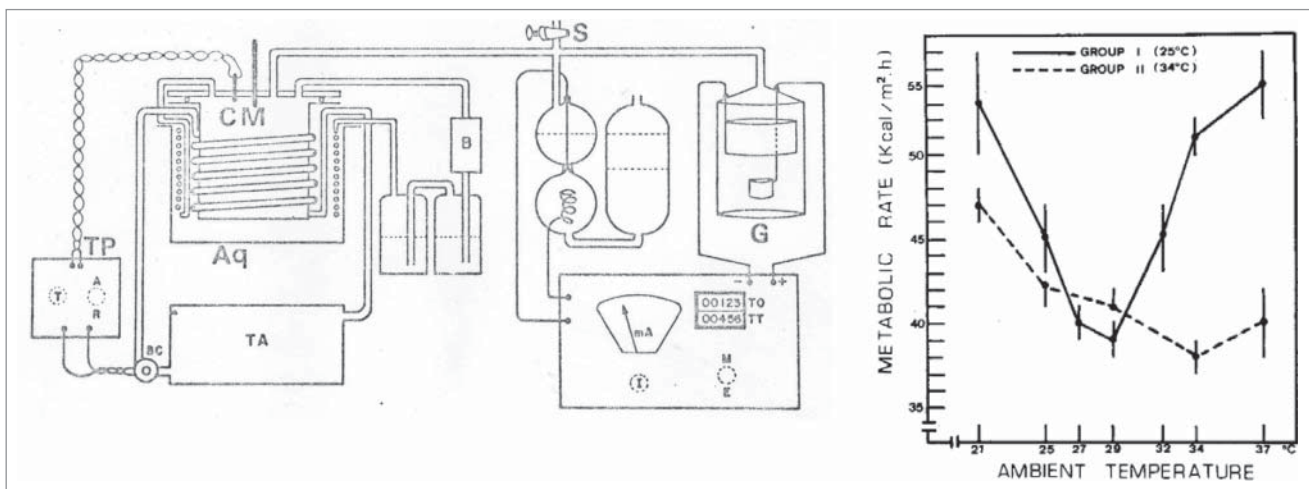
**Figure 4.** Professor José Venâncio Pereira Leite conducting a metabolic study measuring a rat's oxygen consumption using the metabolic chamber in his laboratory at the University of São Paulo, Ribeirão Preto. Courtesy of Museu histórico da Faculdade de medicina de Ribeirão Preto da Universidade de São Paulo.

As already stated, he was one of the researchers involved in the discovery of bradykinin in 1949. There, he mentored 2 graduate students, Frederico Guilherme Graef and Irene Rosemir Pelá, who showed for first time the effects of bradykinin on the central nervous system.<sup>19</sup> Central injection of bradykinin produced a behavioral response, accompanied by vocalization and many autonomic effects, such as bradycardia and hypotension, followed by tachycardia and hypertension. Bradykinin also caused a reduction in

noradrenaline content in the brain stem.<sup>22</sup> After defending her PhD thesis, Pelá has taken a postdoctoral position in Professor Paul Lechar's laboratory in Paris. At the same time, Christiane Gardey-Lavassort was investigating the role of catecholamines in the central nervous system during fever induced by *E.coli* LPS. Pelá, in collaboration with Gardey-Lavassort, published a study indicating the involvement of kinin-like activity in fever.<sup>23</sup> Later, when she returned to Brazil as a faculty member at the School of Pharmaceutical

Sciences of Ribeirão Preto, University of São Paulo, she demonstrated a dose-dependent hyperthermic effect on core body temperature, showing a direct effect of bradykinin on thermoregulation (Fig. 3).<sup>12</sup> In addition, she also showed the participation of kinins in LPS-induced fever.<sup>24</sup> She organized the Laboratory of Thermoregulation and Fever and supervised many graduate students until her retirement. Two new faculty members involved in thermoregulation and fever studies, Glória Emília Petto de Souza<sup>25</sup> and Luiz Guilherme de Siqueira Branco,<sup>26</sup> who has contributed to establish the concept of anapyrexia,<sup>26</sup> were incorporated into the group. The University of São Paulo, located in the town of Ribeirão Preto, is today an important center of thermoregulation and fever research in Brazil.

In the late 1960s, Professor Venâncio Pereira Leite (1920-1980), (Fig. 4) encouraged by Professor Tarasantchi, developed an equipment for oxygen consumption measurement<sup>27</sup> at the Ribeirão Preto Medical School, University of São Paulo. This equipment was widely used for determining basal metabolism in many studies in his laboratory, including that of animals adapted to heat environments (Fig. 5). The oxygen consumption measurements were performed by the coulometric method developed by Professor



**Figure 5.** Left panel: Schematic diagram showing the oxygen consumption system developed by José Venâncio Pereira Leite. Abbreviations: Aq, warming; B, centrifuge pump; CM, metabolic chamber; G, electrolytic oxygen generator; S, tap for ambient communication; TA, auxiliary thermostat; TP, main thermostat; TO and TT, electric timer. Diagram of oxygen consumption system taken from Georgina dos Santos doctoral thesis, with permission.<sup>37</sup> Right panel: Data from the study of dos Santos et al.<sup>28</sup> showing the determination of thermal neutrality in rats adapted to 25°C (Group I) and 34°C (Group II), with permission.

Venâncio,<sup>27</sup> using a closed-loop system with CO<sub>2</sub> absorption and water vapor and continuous replenishment of electrolyte-consumed oxygen. The equipment could be adjusted to maintain the metabolic chamber at a constant temperature with a thermostatic bath. Many graduate students supervised by Pereira Leite, such as Georgina Lobato dos Santos and Marcos Macari, performed experiments using this device. Marcos is considered today an expert and a national reference in the thermal biology of poultry and pigs at the School of Veterinary Medicine of Paulista State University at the Jabotical Campus. Their studies showed that experimental heat acclimatization produced a decrease in basal metabolism similar to that previously observed by Álvaro Ozorio de Almeida and Galvão in humans and animals living in tropical environments.(Fig. 5).<sup>28</sup>

### Thermoregulation in Belo Horizonte: Exercise, Hyperthermia and Fatigue

In 1976, 2 laboratories that would contribute to thermoregulation studies were simultaneously installed at the same campus of the Federal University of Minas Gerais: the **Endocrinology and Metabolism Laboratory**, located in the Institute of Biological Sciences building and the **Exercise Physiology Laboratory** installed at the School of Physical Education, Physiotherapy and Occupational Therapy. Initially, the Endocrinology and Metabolism Laboratory, which performs experiments with murine models in thermoregulation,<sup>29,30</sup> was installed by 3 faculty members: Adelina Martha dos Reis, Candido Celso Coimbra and Umeko Marubayashi (Fig. 6). These three members obtained their PhDs in Physiology at the Medical School of Ribeirão Preto, University of São Paulo. Two faculty members established the Exercise Physiology Laboratory, which employed human



**Figure 6.** The thermoregulatory research group in 2014 (3 assistant professors, postdocs, master's and PhD students) from the Endocrinology and Metabolism Laboratory of the Institute of Biological Sciences, Federal University of Minas Gerais. Courtesy of Professor Candido Celso Coimbra.

models to study hyperthermia and fatigue: Emerson Silami-Garcia, who obtained his PhD at Florida State University and Professor Luiz Oswaldo Luiz Carneiro Rodrigues, MD, a specialist in sports medicine with a PhD in Biological Sciences from Federal University of São Paulo.

In the early 90s, Nilo Resende Viana Lima and Danusa Dias Soares and, more recently, Samuel Penna Wanner started an intense scientific collaboration between the Endocrinology and Metabolism Laboratory and the Exercise Physiology Laboratory (Fig. 7). This collaboration has



**Figure 7.** Photograph taken in 2006 of students and investigators associated with the Exercise Physiology Laboratory (LAFISE) from the School of Physical Education, Physiotherapy and Occupational Therapy of Federal University of Minas Gerais. Courtesy of Professor Samuel Penna Wanner.

contributed to the development of several projects about exercise physiology, temperature regulation and fatigue, elucidating many of the central and peripheral mechanisms involved in the fatigue induced by exercise hyperthermia. These scientists have studied the involvement of the central cholinergic system<sup>31,32</sup> and the participation of central amines,<sup>33</sup> peptides<sup>34</sup> and nitric oxide<sup>35</sup> in the mechanisms of exercise hyperthermia and fatigue. In addition, the Exercise Physiology Laboratory has made important contributions to studies regarding sweating and the physical performance of athletes in the heat.<sup>29,30</sup> Currently, this laboratory has mentored many researchers in thermoregulation, as well as professionals working with athletic performance.

### Final Remarks

Inspired in the idealism and commitment of pioneers, the study of thermal biology in Brazil is well established and has advanced beyond the original centers. Today, there are many centers at different universities dedicated to several fields of thermal biology, fever, exercise, acclimation, chronobiology and so on: University of São Paulo, Federal University of Paraná, Federal University of Paraíba, Federal University of Bahia, Federal University of Juiz de Fora, Federal University of Jequitinhonha e Mucuri Valleys, Federal University of Ouro Preto, Federal University of Minas Gerais, Federal University of São Paulo, Federal

University of Maranhão, Federal University of Uberlândia, Federal University of ABC, Federal University of Viçosa and many other research institutions.

### Disclosure of Potential Conflict of Interest

No potential conflicts of interest are disclosed.

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