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Chapter

Warming in Anorexia Nervosa: A Review

Emilio Gutiérrez and Olaia Carrera

Abstract

Anorexia nervosa (AN) is a severe psychiatric condition primarily affecting young women, and AN has the highest mortality rate among psychiatric disorders. AN continues to be a disorder refractory to psychological or pharmacological treatment. An innovative approach arises from research in rats simultaneously placed on a restricted feeding schedule and given free access to an activity wheel. The detrimental effects of combining diet and exercise in rats can be reversed by a manipulation of ambient temperature (AT). Warming animals exposed to these experimental arrangements reverses running activity, preserves food intake, and enables rats to recover from acute weight loss. This represents a strong preclinical evidence that provides a rationale for a translational approach for the treatment of AN. However, heat application to AN patients was already a recommendation made by William Gull in his seminal paper on AN disorder. A historical perspective of supplying heat to AN patients reviews the circumstances and foundation of this practice. The manipulation of AT in activity-based anorexia (ABA) rats has ended with a period of neglect of AT that parallels the complete neglect of the role of AT in the human AN disorder, either as a risk factor, as a modulating factor in the course of the disorder, or in terms of its utility in the treatment of AN.

Keywords: heat treatment, translational research, ambient temperature, animal research, hyperactivity

1. Introduction

A recent publication analysing the top 100 most cited works on AN reported that only 12 of these papers dealt with treatment, leading the authors to conclude that much work is required to translate 'progress in other areas into effective therapeutic strategies' ([1], p. 13). In contrast to the dearth of literature on treatment, the category encompassing the largest number of papers, 35, addressed the mechanisms underlying the disorder, i.e. 'papers examining diverse theories on AN aetiology and/or maintenance, including family linkage analyses, genetic and heritability studies, biological theories, personality, as well as psychosocial and cultural factors' ([1], p. 10). Moreover, the enterprise of translating theory into effective therapeutic strategies appears to be more challenging than expected. For example, only about 10% of the 4500-word paper, 'Building a model of the aetiology of eating disorders by translating experimental neuroscience into clinical practice' [2], is dedicated to the implications for treatment.

As stated elsewhere [3, 4] given the astonishing contemporary panorama of an absence of psychopharmacological treatments for AN, research with animal analogous models of the human disorder may be helpful in generating new hypotheses for improving AN treatment. A recent example of treatment translation is the reported anxiolytic effect of warmth in anorexia nervosa [5]. In this study postprandial anxiety was significantly reduced in patients resting immediately after lunch for half an hour in a room at 32°C. Bearing in mind the high level of premeal anxiety characteristic of AN patients [6], the significant decrease in postprandial anxiety in warmed AN patients was considerably greater than that achieved by conventional treatments in patients with comparable levels of premeal anxiety such as exposure and response prevention [7].

Interestingly, recent research has underscored the paramount importance of ambient temperature (AT) in the development and more importantly on the reversal of exhaustive running activity, severe weight loss, and self-starvation in rats simultaneously placed on a restricted feeding schedule and given free access to an activity wheel [8–12]. Although self-starvation in rats exposed to this experimental arrangement was first described in the mid-1960s of the twentieth century [13], the term activity-based anorexia (ABA) quickly became dominant describing both the experimental procedure and its resulting behavioural outcome [14]. ABA stands as the best animal model reproducing the main signs of AN (overactivity, extreme weight loss, restricted eating, hypothermia, disturbed sleep, alterations in hypothalamic-pituitary-adrenal/gonadal axis, alterations in diverse appetite-regulating hormones, and severe reductions in grey and white brain matter volume).

Supplying rats exposed to ABA with heat (AT raised to 32°C) reversed excessive activity, improved food intake, and allowed body weight recovery in animals. This reversion was particularly noteworthy as three circumstances concurred in these animals: (a) the increase in AT was delayed until rats had lost 20% of body weight, a point where the spontaneous recovery of rats is unattainable by the animals themselves; (b) animals continued being exposed to the 1.5 h/day restricted food schedule and unrestricted access to the activity wheel; and (c) increased AT allowed for nearly 100% recovery in warmed rats, but there was no single recovery for animals maintained at room temperature (21°C), and a 100% of animals had to be removed to prevent death. This experimental effect of AT has been demonstrated in both male and female animals [10–12].

A more conclusive outcome regarding food intake and body weight was reported in a study [12] where sedentary rats housed at 21°C were food deprived (1.5 h/day) during the first phase of the study that lasted a week. During Phase 2, the animals continued to be submitted to the same restricted feeding schedule for two additional weeks, but AT was increased to 32°C for half of the animals, whereas the other half was maintained at 21°C.

During Phase 2, on average all the animals increased food intake in comparison with Phase 1, but animals maintained at 21°C ate on average 21.5% more than animals housed at 32°C. However, in terms of body weight, only the warmed animals gained a significantly greater amount of weight, and by the end of the experiment, both groups had a similar body weight.

Thus, according to the results, in terms of body weight gain, a warmer environment was more effective than overall food consumption as the buffering effect of higher AT on heat dissipation helped the body weight gain in warmed rats.

In line with this effect of AT on body weight, the same beneficial effect of warming would be expected in AN patients during weight restoration programmes. Moreover, the rate of body weight would be preserved even under a lower caloric supplementation provided that the standard AT of hospital wards was raised. Thus, we should bear in mind the difficulties patients have in gaining weight despite the

elevated caloric intake during conventional nutritional rehabilitation programmes [15] and that roughly a third of ingested calories cannot be processed by patients and are dissipated through elevated diet-induced thermogenesis [16, 17] that further heightens the anxiety of AN patients [18]. Recent data indicate that heat is crucial for reducing anxiety following meals when patients remain in a warmer environment at 32° [5].

Unfortunately, the manipulation of AT in ABA rats has been overlooked [19] which deprived us from recognizing the pivotal role of AT in the fate of rats exposed to ABA. Likewise, AN research has also been susceptible to a conspicuous neglect concerning the role of AT in the human disorder, either as a risk factor, as a modulating factor in the course of the disorder, or last but not least its potential in the treatment of AN.

A historical review of the literature reveals that the suggestion of keeping patients warm is not new, since supplying AN patients with heat was first recommended by William Gull [20]. Undoubtedly, the practice of supplying patients with heat was justified by the evidence accrued by a Swiss physiologist, Charles Chossat (1796–1875), [21] with starved animals.

2. First report of heat for the treatment of AN patients: back to the nineteenth century

Although applying heat to AN patients was first prescribed by William Gull (1816–1890) in 1874, this recommendation has been overlooked for over 140 years. On Friday, October 24, 1873, William Gull first reported the use of an external heat supply to AN patients in his seminal presentation on AN to the Clinical Society of London which was published the following year in the Transactions of the Clinical Society of London [20]: 'I have observed that in the extreme emaciation, when the pulse and respiration are slow, the temperature is below the normal standard. This fact together with the observation made by Chossat on the effect of starvation on animals, and their inability to digest food in the state of inanition, without the aid of external heat, has direct clinical bearings—it being often necessary to supply external heat as well as food to patients. The best means of applying heat is to place an india-rubber tube, having a diameter of 2 inches and a length of 3 or 4 feet, filled with a hot water along the spine of the patient, as suggested by Dr. Newington, of Ticehurst' (p. 24).

Gull's recommendation was based on the early preclinical animal starvation studies performed by Chossat who discovered the healing effects of heat on starved animals. Charles Chossat, a physiologist, physician, and politician from Geneva [22], performed detailed observations on the consequences of starvation in different species. Chossat's main work, Recherches expérimentales sur l'inanition [21], advanced many of the findings now established by experimental physiology on the effects of starvation on the contribution to weight loss by the different organs and tissues in animals starved to death. Thus, Ancel Keys and his colleagues in the Minnesota Starvation Experiment found the quantitative experimental studies of Chossat 'were surprisingly elaborate for the time' ([23], p. 198). Furthermore, in Chapter 9, entitled 'Morphology of Some Organs and Tissues', the authors pay tribute to the work of Chossat in the section 'The History of an Error' referring to the erroneous assertion in the physiology textbooks regarding the absence of cardiac atrophy as a result of undernutrition and starvation in spite of the different findings of Chossat [21] regarding heart atrophy in starved animals.

In the 47-page fourth chapter of Recherches expérimentales sur l'inanition, entitled 'Du réchauffement artificiel', Chossat describes the results of 13

experiments on the warming-up of 26 different animals (17 turtledoves, 7 pigeons, 1 hen, and 1 guinea pig), after being starved close to death. The effects of heat on starved animals shocked Chossat himself: 'I confess that this was not without the vivid satisfaction that I saw an animal arrived in a way by the starvation to the last term of the insensitivity, the prostration and the cooling, to revive somehow, and to retake very quickly a big degree of force muscular and of sensitivity, and it without food, without drink, and without other help than the application of the artificial heat' ([21], p. 595, translated from the original in French).

The first animal to be successfully revived was a turtledove with 35% weight loss and a 23°C body temperature (19° below baseline temperature). As a result of rewarming, Chossat observed that 'The appetite comes back at the animal's inanities that one resuscitates by the artificial warming-up; because one sees them leaving the steams and going to tickle everything that they can meet' ([21], p. 604).

However, Chossat found that the recovery of appetite was not necessarily equal to the recovery of the digestive faculties of the animals, as they could not digest food when artificial rewarming was suspended: 'The digestion takes place, on the contrary, while continuing the artificial warming-up during one sufficient time' ([21], p. 605).

Furthermore, Chossat described the purposeful thermoregulatory behaviour of the animals which actively sought the warm walls of the heater: 'I noticed that as the animals took their strength and their temperature, that they preferred to remain perched more and more on the edge of their steams, a position that they often preserved during several consecutive hours, receiving hardly a small amount of heat. It also happened to them to leave the steams and, when they had gotten more or less cold, often one saw them bringing closer to the stove and to warm themselves against its walls' ([21], p. 615).

Was this the first example of translation from lab findings to human treatment?

According to William Gull's reference to Chossat's work, there is uncertainty as to whether the idea of applying heat to patients in advanced malnutrition was developed in Ticehurst in direct relation to Chossat's studies or whether it was William Gull himself who associated the work of Chossat to the use of a heating device. In any case, regardless of who had established the connection with the work of Chossat, there is no doubt that supplying heat to patients represents the first example of translation of basic scientific findings in a laboratory setting into potential treatments for AN patients.

2.1 Ticehurst Asylum, the Newington's, and William Gull: the first extrapolation of applied heat from animals to humans

Gull's description of warming AN patients in advanced starvation was based on a device employed at the Ticehurst Asylum, which was widely acclaimed in political and medical circles as one of the most successful and highly reputable private asylums in England [24, 25], and Gull was the consultant who completed the required medical certification of some of the wealthy clientele who were admitted to Ticehurst [24]. Ticehurst Asylum was licenced as a private madhouse in 1792, and Samuel Newington (1739–1811), an apothecary and surgeon, was the first Newington in charge of the asylum erected in the grounds of his home, The Vineyard. Five generations of doctors from the Newington family, a 'long established' Ticehurst family since the fifteenth century, owned and managed Ticehurst.

How this heat application method was adopted in Ticehurst Asylum is uncertain, but the inventions of the Newingtons to facilitate the feeding of patients refusing voluntary feeding were inaugurated by Charles Newington (1781–1852), who published the description of 'An instrument invented for administering food

and medicine to maniacs by the mouth during a closed state of the teeth' [26]. According to Charles Newington's obituary as printed in a local chronicle, he was a very ingenious man, and 'Amongst his numerous inventions, was that of an instrument for feeding those who were bent on self-destruction by starvation. This, in its present modified form, is still used, and has never been known to fail' ([27], p. 55). Following the tradition inaugurated by Charles Newington, his grandson Theodore Newington published a description of an instrument developed while he served as an assistant medical officer at the Bethlem Royal Hospital. The instrument, a nasal tube, allowed feeding patients refusing eating without 'the necessity of having to open the mouth, which, with patients with good teeth and strong jaws, is sometimes exceedingly difficult' ([28], p. 83).

The relationship between William Gull and Ticehurst probably commenced after 1871 with his appointment as a consultant physician [29], a period when the asylum was run by Charles Newington's grandchildren, Dr. Herbert Francis Hayes Newington (1847–1917) and his cousin Dr. Alexander Samuel Lysaght Newington (1846–1914, Theodore Newington's brother). By 1873, Sir William Gull had been awarded the title of Baronet for his successful treatment of the Prince of Wales for a bout of typhoid fever. As an influential physician, Gull medically certified wealthy clientele admitted to Ticehurst, and his visit to Ticehurst Asylum in May 1876 was documented with his confirmation of the diagnosis of general paralysis by Hayes Newington [24].

Another unresolved question concerns the paternity of the idea of applying heat to patients. Undoubtedly, William Gull, lecturer in physiology and comparative anatomy at Guy's Hospital from 1846 to 1856 [30], was familiar with the work of Chossat and in particular his work Recherches expérimentales sur l'inanition [21] which was awarded with the Montyon Prix in experimental physiology in 1841 by the Académie des Sciences de Paris.

Furthermore, the successive members of the Newington family running Ticehurst had completed their academic training in prestigious universities including Oxford and Cambridge. The work of Chossat had extensive diffusion in England both in academic circles and even among laypeople. For example, as soon as Chossat's work was published, it was included in 1844 in the 16th volume of *The Edinburgh Medical and Surgical Journal* whose mission was 'exhibiting a concise view of the latest and most important discoveries in medicine, surgery, and pharmacy' [31]. In the same year, the Analytical and Critical Reviews section of June–April 1844 of the *British and Foreign Medical Review; or Quarterly Journal of Practical Medicine and Surgery* [32] included a harsh critical commentary on Chossat's work criticizing the suffering inflicted on the animals. Thus, almost 30 years before Gull's speech before the Clinical Society of London, a direct link had already been explicitly established between Chossat's 'ingenious experiment of placing animals, whose death seemed impending, under the influence of artificial heat' and the application of heat to people suffering starvation: 'This is evidently a point of much practical importance; and the neglect of sufficient artificial calorification, or the too early suspension of it, has doubtless been a frequent cause of the want of success of the means taken to recover inanitiated persons' ([32], p. 354).

Furthermore, the studies performed by Chossat were readily available even to laypeople in England and were extensively commented in the first scientific dissemination book for the general public written by George H. Lewes (1817–1878): *The Physiology of Common Life* [33]. Written the same year as *On the Origin of Species* by Charles Darwin (1809–1892), Lewes' book was first serialized in *The Cornhill Magazine* [34]. Chapter VII of Volume I, entitled 'Why we are warm, and how we keep so' ([34], pp. 281–315), includes a detailed description of Chossat's starvation experiments that Lewes concluded 'are well known and the results are

accessible in almost every text-book' ([34], p. 352). Chossat work was once again reported in *The Cornhill Magazine* [35], mostly read by laypeople in England. The 1861 Russian translation of *The Physiology of Common Life* made a profound impression on the adolescent Ivan Pavlov, who as an elderly man could still quote long sections from it [36].

However, regardless of whether it was Gull or one of the Newingtons who was acquainted with the work of Chossat, the question remains as to why the application of heat was not maintained as a standard strategy and vanished as a treatment for AN patients. Gull's lecture was widely echoed in publications. On November 1, 1873, 1 week after his speech before the Clinical Society of London, the discussion by the attending physicians was included in the Report of the Societies' section in *The British Medical Journal* [37]. The report in *The British Medical Journal* also appeared across the Atlantic in what was to be the last edition of *The Half-Yearly Abstract of the Medical Sciences* published in Philadelphia in 1873 [38].

Although there were several references to the relevance of warming for the treatment of AN patients in the years following Gull's 1874 paper, the interest appears to have waned by the turn of the century. One of the last mentions appeared in the editorial of *The Lancet* issued a week after what happened to be Gull's last publication, a case note of a patient with AN stating 'The cure consists of three things—rest, warmth, and the regular and frequent introduction of food, in utter disregard of the anorexia of the patient' ([39], p. 584).

As far as we are aware, despite the clinical bearing mentioned by Gull, we have found no justification for abandoning his specific recommendation, either founded on its verified clinical uselessness or due to a theoretical reasoning that would render it obsolete or any other reason for it falling into disuse. A plausible explanation is that the initiation of forced feeding displaced the use of heat. As mentioned elsewhere [40], during a 63-day time span following Gull's last publication in 1988, a total of eleven articles appeared commenting Gull's last paper, of which four mentioned force feeding as the optimal strategy: 'forcible administration of nourishment so very simple a process that there need be no hesitation in resorting to it when necessary; these are at once safe and effective, and by their means nutrition can not only be carried on for an indefinite length' ([41], p. 597). Forced feeding had already been voiced by two doctors (Dr. Williams and Dr. Edis) during the discussion that followed Gull speech before the Clinical Society of London on October 24, 1873, but there was no mention on the employment of heat or to Chossat in the minutes of the meeting reported in *The British Medical Journal* [37].

One of the last mentions of the use of heat in the nineteenth century appeared in the first documented necropsy of a patient who died of self-starvation, which noted that all efforts were made to maintain her warm even by wrapping the patient with bandages [42].

In the twentieth century, references to warming AN patients were scarce. Dejerine and Gauckler refer to warming in their treatise *The Psychoneuroses and Their Treatment by Psychotherapy* when they stated 'It may happen that, among certain patients who are extremely weak, one is obliged to seek for aid from ordinary medical therapy; one may thus to give injections of serum, or hypodermics of caffeine, or camphor oil, to warm the patient by artificial means' ([43], p. 321). In 1931, a clinical report [44] informed a treatment of a series of 20 cases of functional anorexia treated at Ruthin Castle, a private hospital (1923–1950) for the investigation and treatment of obscure medical diseases [45], in which patients were kept in bed in a warm room (although the recommended room temperature was unusually low, 60°F, for today's standards). Likewise, in the same decade, two German psychiatrists [46] mentioned in their report on the treatment of a 17-year-old girl the use of heating pads and an electric blanket for heating patients. Later, the use of

electric blankets was considered by psychoanalysts not on face value but as a regressive substitute of the umbilical cord: 'Our patient who lay in bed curled up 'attached' to the wall via the electric cord of a heater resting on her abdomen' ([47], p. 395). Furthermore, this blurring of warming is evident in the only figure that appears in Selvini-Palazzolli's book, *Self-Starvation: From the Intrapsychic to the Transpersonal Approach to Anorexia Nervosa* [48]. On page 65 there is an illustration of the analysis of a dream (the ugly yellow dog's dream). In the picture drawn by the adolescent, she appears sitting on the floor covering her mouth while her mother looks from behind a hole in the wall. The girl's back rests on the radiator of the wall, an aspect that is not mentioned at all in the psychoanalytic interpretation.

In relation to the historical journey regarding the use of heat as an adjunctive treatment for AN patients, it is worth noting two spontaneous improvements due to febrile conditions reported by Lasègue [49] and Weizsäcker [50].

Since then, as far as we are aware, we have had to wait until the end of the twentieth century to see the reintroduction of the use of heat in three cases treated with three different strategies of heat application: continuous exposure to a warm environment, wearing a thermal waistcoat, and sauna baths in an infrared cabin [51]. Besides putting an end to the long period of persistent disregard for the role of AT in AN, this paper demands a place for ABA research in AN treatment development.

3. Uncovering the neglected role of ambient temperature in anorexia nervosa

With the exception of research on the effect of season of birth on the subsequent development of anorexia nervosa, AT has been neglected by researchers [52]. However, the first reference to the probable relationship of AN and AT appeared in an editorial in *The Lancet* on March 24, 1888 with a commentary on the paper published by W. Gull on AN that appeared the preceding week in the journal: 'Most of the cases seem to occur in the colder months of the year, and possibly this may be more than a coincidence' ([53], p. 584).

There is growing evidence that AT merits more attention in future research given its paramount importance with respect to several relevant signs of AN such as hyperactivity, body weight, and amenorrhea. Furthermore, there is indirect evidence that the world incidence of the disorder is bound not only to culture but to latitude too [54].

The relevance of AT on the body weight and physical activity of AN patients was first revealed in a study in which adolescent patients with AN showed significantly higher physical activity during the colder months of the year, October to April, than in the warmer months, April to October [55]. In contrast, patients from the warm group were less underweight than those of the cold group. The relationship between AT and physical activity was confirmed by analysing a subset of eight patients with a temperature difference of 6°C on two consecutive days during the monitoring of the patients' physical activity. The physical activity of these patients was significantly higher on colder days, confirming the modulating role of environmental temperature over physical activity beyond the eventual regulatory function of anxiety and negative effect or relevant dimensions of eating psychopathology as body dissatisfaction and drive for thinness. This within subject analysis discarded that the association between AT and activity was mediated by other climatic aspects associated with AT, such as day length or seasonality. It is remarkable that the greater activity of ANR patients during the winter months contrasts with that reported at temperate latitudes for normal body weight people where physical activity decreases in the colder months of the year [56].

Related to the finding of lower body weight and BMI in AN patients during the colder months of the year, a retrospective study covering admissions during a 3-year period (2007–2010) of an adolescent inpatient eating disorders unit revealed that AT was a modulating factor in body mass index (BMI) at hospital admission [52]. The study revealed that AN restrictive (ANR) subtype patients differ from AN binge/purging (ANB/P) subtype patients with respect to the body weight fluctuation pattern throughout the year. The study revealed that differences between both diagnostic subtypes only occurred during the cold semester, revealing that the differences were due to the inverted annual pattern of body weight fluctuation in both groups of patients. Thus, while annual fluctuations in the weight of ANB/P patients were similar to those of the general population, i.e. having a higher BMI during the colder months of the year and a lower one during the warmer months [57], the pattern for ANR patients was the opposite.

Bearing in mind the above, it is hardly surprising that, in comparison to the warm semester, ANR patients admitted to hospital during the colder season had a longer hospital stay, a finding which has been inconsistently replicated in two different German samples [58, 59]. Moreover, due to their lower body weight during the cold semester, ANR patients had longer hospital stays than ANBP patients [52]. Moreover, other researchers have provided strong evidence of the effects of AT on menses recovery in AN patients. During the warmer months of the year, probability of menses recovery was twice as high as in autumn or winter, despite the fact that body weight of the patients were 2 kg less in the warm season than in the cold season, which was directly associated to lower energy expenditure associated with thermoregulation in the spring and summer months [60].

A possible explanation for this pattern of higher activity and lower body weight in AN patients was advanced [19] as a dramatic example of the energy balance equation in which AN patients are locked up. Given their restrictive eating pattern, the lower the AT, the greater the weight loss and consequently the greater the increase in physical activity as a potential surrogate thermoregulation mechanism. However, as ABA research has shown, resorting to increased motor activity raises the body temperature in the short run, but the mobilization of fat reserves to maintain activity which supposes a reduction in body insulation. Moreover, deficient insulation resulting from reduced subcutaneous fat in AN reduces protection against environmental hazards as Arthur Crisp pointed out that 'Fat has general biological purposes as a reserve of energy and a contributor to body temperature regulation, both as a component of resting metabolic rate and, subcutaneously as insulation' ([61], p. 481). Thus, all other things being equal, given the stable restrictive energy intake of ANR patients, a colder environment would impose a greater demand for the maintenance of body temperature. In this scenario, increased physical activity would perform a thermoregulatory function rather than being driven exclusively by psychological factors such as excessive preoccupation with body weight and shape [62].

Besides the aforementioned influence of AT on the hyperactivity and body weight of AN patients, there is also an underreported active search for heat by AN patients. For example, this was the case with the conspicuous absence of reports in the literature of sauna baths as a weight-losing strategy among AN patients [63]. This complete absence of reports contrasted with spontaneous mentions of the use of sauna baths AN patients in their chats on the Internet [64]. It has been suggested that among the possibilities underlying the absence of reports of the use of saunas, there was a possibility that regular sauna bathing may either act in preventing predisposed adolescents from developing the 'full-blown' syndrome or accelerating recovery from AN [63]. Hence, it may be more than mere coincidence that in Finland, where saunas are a substantial part of Finnish culture, the 5-year clinical

recovery rates for DSM-IV anorexia nervosa were as high as 68.4% in patients undetected by the health-care system [65].

Furthermore, there is evidence that the world incidence of the disorder could be bound not only to cultural influences but to climate and latitude too [54]. This seems to be the case according to the results gathered by means of a bibliometric perspective where the worldwide distribution of scientific publications was deemed to be an indirect indicator of the incidence and prevalence of the disorder at different latitudes. Two subsequent studies [66, 67] have reported that the distribution of references for anorexia nervosa have remained considerably stable over the last 25 years, associated to higher but not extreme latitudes and to climates with regular seasons with no severe temperature variations across seasons. Thus, references to AN condense into a 40–55° latitude range in the Northern Hemisphere which closely parallels with the vast majority of epidemiological studies undertaken on populations living in this latitude range in the Northern Hemisphere [68].

4. Conclusion: listening to Hippocrates (460–377 BCE)

One of the most important treatises in the *Hippocratic Corpus* entitled *On Airs, Waters and Places* wisely begins with 'Whoever wishes to pursue properly the science of medicine must proceed thus. First, he ought to consider what effects each season of the year can produce; for the seasons are not at all alike, but differ widely both in themselves and at their changes' ([69], p. 71). Without any reasonable doubt, AT has been systematically overlooked in AN research, which has hindered a better understanding of the use of heat in the treatment of AN.

Acknowledgements

The preparation of manuscript and research reported was supported by the research budget of the Unidad Venres Clinicos (University of Santiago de Compostela). The funding sources had no involvement either in the writing of the manuscript or in the decision to submit the paper for publication.

Conflict of interest

The authors declare no conflict of interest.

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