

Balneotherapy: from basic research to clinical challenges

Cantista P⁽¹⁾

⁽¹⁾Centro Hospitalar Universitário do Porto, Porto (Portugal)
pedro.cantista@gmail.com

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SOME THOUGHTS ABOUT THE SCIENTIFIC "PROOF" IN MEDICINE

When we want to discuss what the "proof" in science consists of, we are automatically transposed into the philosophical field. I'm convinced that when we speak of knowledge we cannot escape from the ancestral dialectic philosophy / science and pass through the successive thoughts and arguments of philosophers and scientists.

There is obviously a historical evolution of epistemology. From Metaphysics to Logic, from Rationalism to Empiricism, from Positivism to Structuralism, human knowledge evolves in a flow of successive acquisitions brought to our minds by diverse methodologies, with which humanity continually seeks the Truth.

Nowadays, thought is closely linked to technological evolution, influencing the scientific method for an ever closer approximation to mathematical rigor and to the utopia of certainty. Far away seems to be the "methodical doubt". Automatic information (informatics) dominates and constraints thought.

Sometimes we forget that the Scientific Method is not in itself a unique way of proceeding, but rather than a model of thought aims, to guide the investigation, formulated in the hypothesis, by obtaining and discussing experimental data that may lead to possible conclusions. We want exact science. However, in 1927 Werner Heisenberg, introducing the concept of the "uncertainty principle," sets a limit on the accuracy with which certain pairs of properties of a given physical particle, known as complementary variables (such as position and linear momentum), can be known. Although the principle of uncertainty may have its validity restricted to the subatomic level, by inserting values as indetermination and probability into the field of empirical experiment, this principle constitutes a fundamental epistemological transformation for modern science.

Will there be exact sciences? Is this question wrong because of its apparent contradiction? Or is there really no exact science or absolute certainty?.

With regard to the so-called "medical sciences" it seems unquestionable that the infallible determinism of an immutable cause-effect relationship is far from reality. That is why it is so often said: *"death is the only certainty of our life ..."*

Is medicine a science that simply aims and is exhausted in the diagnosis, prevention, treatment and rehabilitation of diseases, through the application of a set of techniques, or still remains an art, as it was considered by many old masters? In Medicine what is more important: the experimental data converted into "knowledge" or the true "wisdom" that includes the very attitude of calling into question the "facts" of "evidence"? Against facts there are no arguments or precisely against "facts" there are arguments?.

Carrying these reflections into the daily life of our scientific "production", I would say that in our time the knowledge in Medicine comes from the so-called "basic sciences", essentially data from the "laboratory", which aim at understanding biological, physiological or pathological phenomena. This knowledge allows us to formulate therapeutic hypotheses whose adoption, implementation and regulatory institutionalization follows from a translational scientific process, concluded by pragmatic clinical trials, validated by probabilistic methods (mathematical demonstrations). So we fall into reality and instead of "causality" we stand by "probability".

In this subject we cite Sir Austin Bradford Hill who in 1965 published a set of criteria to evaluate if an association could be considered as causal. These include strength, consistency (observation at different times), specificity, temporality (cause precedes consequence), biological gradient (dose-response relationship), plausibility (consistent with biological evidence), consistency, experimental evidence, and analogy). The evaluation of the existence or not of association and of causal relation, must comprise two fundamental aspects: the identification of the effect and its quantification.

Several models of study are developed. Studies without control group (individual cases or individual case sets) and studies with control group; case series studies without randomization (case control, cohort) or randomization (clinical trial, community trial). The studies with control group allow a direct and objective comparison between the group under study and another group that will not have the same characteristics in appreciation.

The random distribution of study participants, which we call "randomization", forms the basis of the trials considered to be of the highest degree of evidence, the so-called randomized controlled trials. We generally adopt the acronym of the English designation when we intend to refer (RCTs - randomized controlled trials).

In this process, in order to homogenise the groups, each participant should have the same probability of integrating each of the groups formed, trying to isolate the variable that we want to evaluate (in most cases the intervention in question).

In the observational studies we included the cohort methodology studies, which may be prospective or retrospective, where the cause precedes the effect and that starts from the identification of the presence or the absence of exposure to the factor in question. Observational studies are those of case-control methodology. These are retrospective and in them the effect precedes the cause.

Based on the pragmatic studies, there is the challenge of many usual clinical attitudes and interventions, considered to be true and beneficial. The so-called "Evidence-Based Medicine" (EBM) was born, much influenced by Archibald Lemman Cochrane (1909-1988), who introduced these "randomized studies", that is, therapeutic trials in which a comparison is made between groups of participants (random), whose results are applied statistical methods. The conclusion will not be 100% accurate, but it tends toward that percentage the stricter the study design and the larger the sample size, which means the number of participants in a given trial.

Depending on the design of the clinical trials (retrospective, prospective, longitudinal, cross sectional, controlled, uncontrolled, single or double blind, randomization, etc.) and their conclusions or, where possible meta-analysis of data from various studies), a "level of evidence" can be established, hierarchically positioned in a graded classification, whose representative image is the well-known "pyramid of evidence".

The level of evidence reached in a given hypothesis determines according to this classification a "degree of recommendation" that guides clinical behaviour, aiming to condition medical performance in an established model of "good practices".

SOME THOUGHTS ABOUT THE SCIENTIFIC "PROOF" IN CRENOTHERAPY

If we want to ask how we can establish a Scientific Evidence in Thermal Medicine, what lessons can we draw from what has been exposed? Should we base our knowledge only on results from clinical trials? Without them can we say that the therapeutic use of natural mineral waters, steam, thermal gases and peloids lacks any scientific basis and as such is only a traditional practice with no place in modern medicine? Should we undergo a thermal treatment such as a drug and submit it to the demanding sieve of a prospective, randomized, double-blind, longitudinal trial with a significance level of at least 95%?

Obviously this is not possible. And it is not possible because this model is not applicable. Do not order an RCT for a surgical, psychotherapeutic, or for many Physical and Rehabilitation Medicine techniques. There are medical procedures for which the same methodology applied to drugs is not possible. How to proceed to establish the therapeutic indications of natural mineral waters? We lack scientifically-developed medical-hydrological studies, of course. Prior to any test, the classification of new natural mineral waters is required. We start from this premise and can

investigate in laboratory the influence of physical, chemical and biological factors on the physiological and pathological mechanisms, constructing hypotheses to be demonstrated by the clinical trials. This raises the need to establish appropriate methodologies for the agent or process in question. Given this step, in order to respond to the claim of the dealers to add new therapeutic indications in waters already qualified as natural minerals, I would say that a better definition of these therapeutic indications is necessary. But let's not fall for fundamentalisms. The present non-existence of a test does not mean that a particular practice is invalid or does not act. We should be critical, but use common sense. The proof has not yet been produced, perhaps because we have not yet obtained a method for its demonstration.

Can EBM be applied to crenotherapy? Clinical evidence can only be proven for an agent, an application form or a health condition. However, most therapeutic agents cannot be subjected to double-blind trials. On the other hand, it is necessary to take into account that thermal therapy is usually complex, that is, it adds to the effects of mineral water or other crenotherapy agent, climate, diet, physical and psychological relaxation, physical activity and social interaction. That is: contextual factors (environmental and personal). In the investigation of the medical field in crenotherapy are essential elements:

- 1) Natural mineral waters (Na, Ca, Mg, Cl, SO₄, H₂S, CO₂), gases (CO₂, H₂S, Rn), peloids, climatic factors and other therapies (massage, diet, physiotherapy, psychotherapy).
- 2) Modes of application: oral ingestion (hidropinia), baths, showers, ablutions, steam techniques, irrigations, sprays, sprays, inhalations, injections, enemas, etc.
- 3) Dosage: simple use, series, combinations.

Regarding the type of clinical trial and validation criteria of the studies, much has been discussed. The subject has been the subject of wide international debate. In France, where the production of evidence for a particular therapeutic intervention determines its reimbursement by the state, this problem was studied by the National Academy of Medicine (XII Commission). His conclusions, which were the responsibility of the academics Patrice Queneau, Bernard Graber-Duvernay and Claude Boudène, were presented for the first time on 24 January 2006. Subsequently, the criteria required for a favourable opinion of the French National Academy of Medicine were updated. Because we think that this conclusions should serve as a model we mention them here.

P. QUENEAU, JP NICOLAS, R. TRÈVES, C-F. ROQUES

Commission XII, National Academy of Medicine, 16 rue Bonaparte, Paris, 7ème

According to the French law, the National Academy of Medicine has to establish the benefit for health of the natural mineral waters.

Therefore, the academy gives advices to the government in different situations concerning balneotherapy such as the authorization of a new resort, a new spring (new water), a new medical orientation, a new thermal care. The opinion of the academy will be based on scientific data produced by relevant clinical studies which have to meet recently updated criteria:

- *The data produced must be based, at least, on one clinical prospective study.*
- *The trial has to concern a specific condition with exclusion and inclusion criteria.*
- *The trial, controlled or uncontrolled, will be implemented according to the rules of the clinical trial good practices (and the legal requirements).*
- *The number of patients will be determined according to the methodology and the expected outcomes.*
- *The thermal (and the control) treatments will be clearly established, described, delivered and reported.*
- *The assessing investigators will be blind of the treatment delivered to the patients.*
- *The main endpoint will be quantifiable and assessed at least at 6 months; secondary endpoints, eventually medico-economic ones, will be also considered.*
- *The protocol will be elaborated by a scientific committee including a scholar expert of the condition, an expert in the methodology of clinical investigation, a doctor of thermal resorts; all will disclose their competing interests.*
- *The advice of an ethic committee is required.*

To appreciate the results of the trials provided by the petitioners, the academy will pay a particular attention to the satisfaction of these different criteria in the studies.

In Portugal, with the publication of Law 142/2004, a new Health Ministry Technical Evaluation Committee was created within the scope of its article, which, under the Chairmanship of Prof. Frederico Teixeira, came to establish a Regulation of "Norms and Criteria for Thermal Research" (New Therapeutic Vocations / Evidence of Therapeutic Effect). We had the opportunity to collaborate in the elaboration of this document whose contents do not differ conceptually from the idealized by the French Academy. Both documents appear at the same time and curiously the two have been updated in the same periods. We are of the opinion that these standards provide sufficient scientific basis for a legitimate crenotherapy prescription and for

its fair inclusion in our public health system. With this we do not want to dispense with the thermal activity of better and more thorough scientific and clinical research.

I will conclude with one last thought. Perhaps a much repeated idea but still much forgotten by the undefeatable defenders of EBM. I insist that the Guidelines are for diseases and not for patients. Understanding the individuality of the patient is an integral part of the art of medicine. Already two thousand years ago Aurelius Cornelius Celsius stated that the doctor should apply the general knowledge in his patient, but also attend to their individual characteristics, even if this attitude may be contrary to pre-established principles. Attention to the patient's individuality makes all the difference in the quality of the practice of medicine. EBM data cannot be dogmas. The medical act results from a much wider set of references. It incorporates beyond scientific knowledge, experience, wisdom, common sense, morals, ethics and deontology. I therefore advocate that crenotherapy should remain a Medical Act.

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