

Implantation Failure

Alberto E. Tersoglio★, and Dante Roberto Salatino★★

About the author(s)

★Alberto E. Tersoglio: Founder, and Director of the International Assisted Reproduction Center. Director of the Academic Unit of Molecular Biology dependent on the National University of Cuyo, Mendoza, Argentina. Email for correspondence: tersoglio@gmail.com

★★ Dante Roberto Salatino, Researcher of the Institute of Philosophy and of the Institute of Linguistics - Lecturer in the General Psychology Department - Lecturer in the Philosophical Aspects of Physical-Mathematical Science Department - Faculty of Philosophy and Letters - Teacher and Researcher in Artificial Intelligence in the Mechatronics Career - Faculty of Engineering - National University of Cuyo, Mendoza, Argentina Email for correspondence: dantesalatino@gmail.com

ABSTRACT

The purpose of this paper is to show the usefulness of an alternative scientific argument based on Transcursive Logic in the natural science, such as medicine. The auxiliary methodology was applied to determine the role of a polyvalent endometrial treatment in patients suffering from ‘repeated implantation failure’ in an ovodonation program. Secondly, this paper analyzes changes in the leukocyte endometrial population. We proposed a way of systematizing the process of embryo implantation and of scientifically addressing the repeated failure of implantation through adduction. This paper considered the dynamics of the natural and altered biological process and are evaluated the empirical results, beyond statistical findings. (Tersoglio & Salatino *et al.*, 2015).

Keyword: In vitro fertilization, Repeated implantation failure, Research methodology, Transcursive Logic.

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1. INTRODUCTION

This paper addresses an important aspect of reproductive health, such as infertility affecting 15% of couples and where 40% of are attributed exclusive female factor. We analyze infertility caused by repeated implantation failure that cannot avoid a viable natural pregnancy and the failure of assisted reproduction methods.

We give some details on normal gestation, especially related to immunity. The immune system is a set of innate biological structures and processes that help an organism to maintain internal balance, adapting to external aggressions and combating internal aggressions.

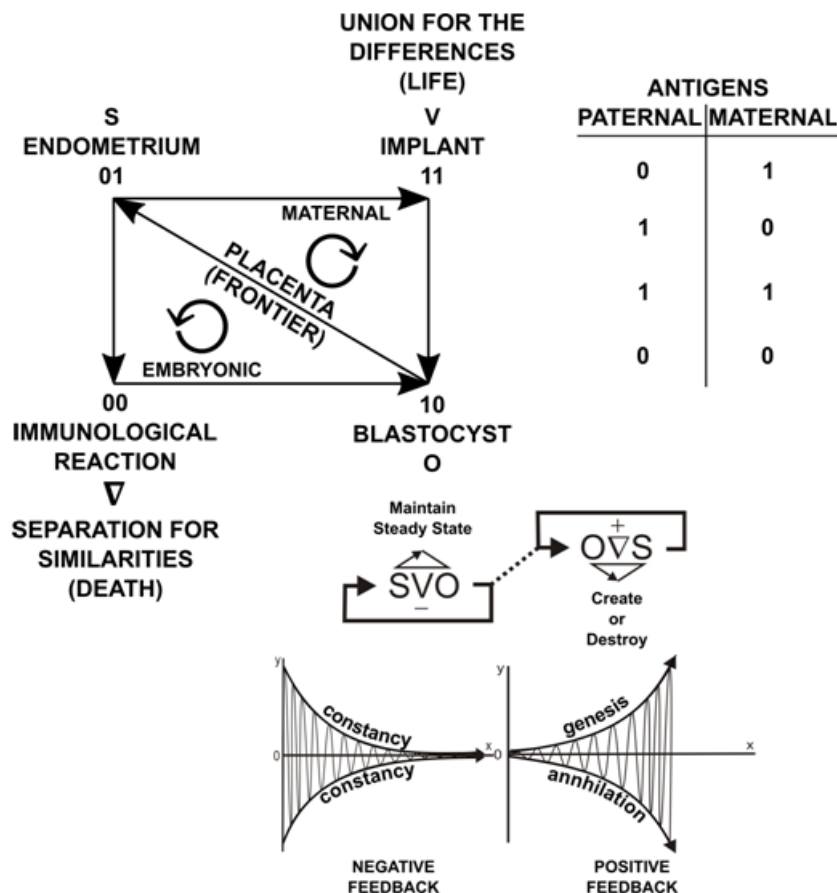
The innate response occurs when a foreign agent or an alert signal is identified by ‘pattern recognition receptors’ (Medzhitov, 2007). The defenses of the innate system are not specific, and although it is the dominant system of protection in most organisms, it does not confer lasting immunity.

Immunological recognition and signaling between cells of the immune system is in charge of a molecular complex called the ‘human leukocyte antigen’ (HLA). The ways in which it is transmitted from parents to children constitute a system called ‘histocompatibility complex’, used to distinguish the own from what is not.

The embryo presents a 50% difference in its ability to modify the HLA-related immunological behavior of the pregnant mother. Since the mother only recognizes half of the embryonic tissues, it would be possible for the presence of a specific immunological reaction by rejection, with the death and expulsion of the embryo. However, this usually does not occur, because the mother develops some immune tolerance towards the product of gestation. This tolerance is a consequence of the production of certain immunosuppressive factors (substances that prevent the rejection of foreign tissues) that act in the uterus.

Following the proposal made by the Transcursive Logic, we propose a possible scenario where nesting of the embryo in the uterus can occur. (Figure 1).

Fig. 1: PAU of implantation



If we analyze the codes of the PAU (Universal Autonomous Pattern) (Salatino, 2017) in Figure 1, we see that the presence of paternal and maternal antigens defines the situation in which

fundamental elements involved in the implantation are found. Thus, the endometrium is characterized only by maternal antigens (01). The blastocyst is represented by the paternal antigens (10). The implant is determined by the relational confluence of the two previous ones (11). On the other hand, the immunological reaction that can harm the embryo does not depend on the genetic contribution of either parent, but on the release or non-release of immunosuppressive substances in the uterus (00).

Embryo implantation is performed if tolerance to maternal-fetal differences is achieved. Repeated superficial cycles (dextrorotatory) given by the relationships between the endometrium and the blastocyst allow the development of nesting and also the placenta. Its fundamental mechanism is negative feedback (error correction), which, as shown in the previous diagram, tends to a steady state.

When these accumulated differences reach a certain threshold, the maternal immune system is put into operation, which tends to eliminate the 'foreign object' represented by the implanted embryo. For the blastocyst two alternatives emerge: a) adapts and increases its complexity according to the new requirements (tolerance of similarities: uterus and blastocyst are organic tissues) now protected by an immunosuppressant, or b) dies (is expelled) achieved a balance by not recognizing the mother (intolerance of similarities), not even their own antigens, which are considered to resemble the invading agent (paternal antigens). This, by not being tolerated, leads to the liberation of the blastocyst, or the death by detachment from the embryo.

The mechanism that activates the whole process is a positive feedback, which as we see in the scheme, allows either creation (genesis) or annihilation (destruction). If the blastocyst dilemma is solved favorably, that is, if the profound cycles (levorotatory) given between the blastocyst and the endometrium by an immunological reaction are solved by morphogenesis, everything begins again. The superficial cycles are resumed, but now with a more complex blastocyst that has to face new challenges, even to new immunological 'defiance'.

Among new organs developed is the placenta. It constitutes the functional limit that separates, but at the same time it unites the maternal or proper (that integrated during the superficial cycles), of the considered embryonic or foreign (incorporated in the profound cycles). This organ behaves like an active unit of double identity, since simultaneously it means distinction and belonging and therefore, at the same time, opening and closing.

A filter that lets pass (nutrients, oxygen, hormones, etc.) but at the same time brakes (harmful substances). In it, the union and separation concur. Functionally it is a 'bridge' between the mother (the superficial) and the embryo (the profound), that if gestation continues its course will become a fetus. It allows the existence of a contexture or protected area before the defensive immune aggressions of the mother.

2. LITERATURE REVIEW

1 – *“Semiotic of the real systems. Semiotic analysis of the emergency psycho-bio-sociocultural as method of observation of the natural language.”* (Salatino, 2009 - Doctoral Thesis).

In this work, it is considered to be the study of the natural language from observation. By which we can determine, without conditionings, his reality, his rooting to the living thing, to the subjective thing, what aspects of the reality of the man is capable of reflecting and how it does it. The intention is to contribute a method that allows the discovery of laws that according to the subjective thing, allow a study of the production / comprehension of the language. This analysis employed an original tool called Transcurssive Logic (logic of the sense); on the one hand, to tie the reality of the language to the whole reality and for other, to demonstrate by means of the abductive analogical method, the possible existence of a 'universal language'. We also, compare the phylogeny of the central nervous system with the proposal for the language, remains firmly established the biological and evolutionary character of the natural language. From the semiotic of the emerging psycho-bio-sociocultural, it was possible to consider the subjective aspects of the symbolic human language, a determinant at the time of understanding what is the language and in a derivative way, to

demonstrate that the natural human language and inside him, the different languages, there are a product of a genetic evolution that show an evolutionary variability.

2 - *Repeated implantation failure in oocyte donation. What to do to improve the endometrial receptivity?* (Tersoglio, A. E.; Salatino, D. R. et al., 2015)

We determine the role of polyvalent endometrial treatment in patients undergoing IVF-ET who had recurrent implantation failure (RIF) in a program of oocyte donation (OD). The results were expressed in terms of live birth rate (LBR). Secondly, analyze changes of endometrial leukocyte population evaluated by flow cytometer (FC) and histopathology. This work, used for the first time in a natural science the Transcursive Logic as a complementary research method, through a prospective study of a model-based control with analog abductive methodology.

3 - *Treatise of Transcursive Logic. Evolutionary origin of the sense in the subjective reality.* (Salatino, 2017)

Transcursive Logic (is defined as TL): a tool, it is the only one that allows us to deal with the evolution (passing) of the subjective aspects of any living being, including man, in which both the volitional and the cognitive aspects are covered. TL is a dynamic, non-inferential, quaternary and policontextual relational model that operates with ontological niches (continents) assembled according to a universal language structurally defined, by a Group (as a relational entity), and functionally by a Galois Connection (as composition of opposites and complementary). This model is based on the change or transformation that emerges when the compelled components of subjective reality, that is, subject and object, are interrelated. This change or transformation occurs in two simultaneous levels: a) superficial and apparent of discrete nature and what we will call 'content', and b) the profound and hidden of a continuous nature that we will know as 'continent'. As a research method: it links the theoretical knowledge and the empirical knowledge, with its discovery and validation, in this way it is adapted to the scientific knowledge that is intended to be achieved, thus, making possible the validation of what is discovered. At the superficial level, it behaves as an analogical-abductive method. Starting from the results, one searches for a conclusion or hypothesis, separating two levels of analysis: known or evident (superficial) facts and unknown facts (profound), from which they are assumed to behave similarly. At the deeper level it behaves as an analogical-adductive method by bringing the two previous levels closer together, making them simultaneous, contrasting them against a model taken from everyday reality. The strategy implemented has as its substrate, to dispense with the frame of reference, to be able to form an (algebraic) group with the relationships between the fundamental elements that characterize the system under study. In this way, the syntax of a 'Universal Language' is achieved and allows us to approach any branch of the science and of the humanities.

3. MATERIAL AND METHOD

We will deal with the repeated failure of this mechanism in ovodonation. In 2015, 75 patients with repeated implantation failure in ovodonation were studied. (Tersoglio, Salatino *et al*, 2015.) In this paper, the conditions that an endometrium had to meet were addressed in order to make the implant successful, the most important factor in these patients was endometrial receptivity. In order to achieve this objective, it was necessary to exclude the embryonic quality (assuming as optimal, according to international criteria) as the only predictor of implantation and pregnancy. Only two elements were considered relevant: 1) the need for an adequate endometrium that would allow implantation and 2) the therapeutic availability to correct those parameters that impair its quality.

The theoretical scenario where the research was framed has to do with the immunological aspects put into play at the time of implantation. The observation and analysis of the embryonic conditions for a successful implant only contributes, a small part to the explanation of the implantation fault. This assertion is based on a superficial and apparent observation, which quickly

accredits the simple empirical rule ‘cause - effect’ and allows to formulate ‘objective laws’ that may have *a priori* some opportunity to be true.

The justification of the study was to try to find some principle expressed in terms of immunological mechanisms (hidden) that could take into account a fundamental factor in the implantatory equation: the endometrium.

We developed as a central hypothesis the possibility of increasing successful ovodonation results if the alterations detected in the endometrium were corrected through specific therapeutics. As a secondary hypothesis, the endometrium is proposed as the most important factor for a successful implant.

The main objective of the study was to analyze morphological and functional changes in a population presenting ‘repeated implantation failure’ (RIF) through a study of the endometrial lymphocyte population. This was done before and after specific treatment. The results were compared in those cases where a clinical pregnancy was obtained that culminated with a live birth. (Ibid, p. 47)

As secondary objective of this investigation was the possibility of establishing a set of techniques necessary to make a correct diagnosis of the situation and to be able to establish a suitable treatment to correct possible alterations.

If only the hypothetical-deductive method had been adhered to in this work, we could say that it was a case-control study, ambispective, and quasi-experimental. However, as the abductive method was used as adjuvant, we can say that it is a prospective control study based on a model.

The abductive method (created by Peirce (1878), enlarged by Samaja (1999) and completed by Salatino (2009) which Salatino called *adduction*) is the one indicated when an investigation starts from the results, as in the present case, and the interest of the study is centered on a particular element of the system being analyzed. Here, that element is the endometrium.

Using traditional methods there is no way to isolate an aspect to analyze its behavior, without altering the whole system and stop responding to the rules already established and accepted for its operation.

Since abduction, the immune response in the endometrium has been transformed into a ‘hidden model’. From this model we need to find some unknown facts of its behavior, starting from known facts (the results).

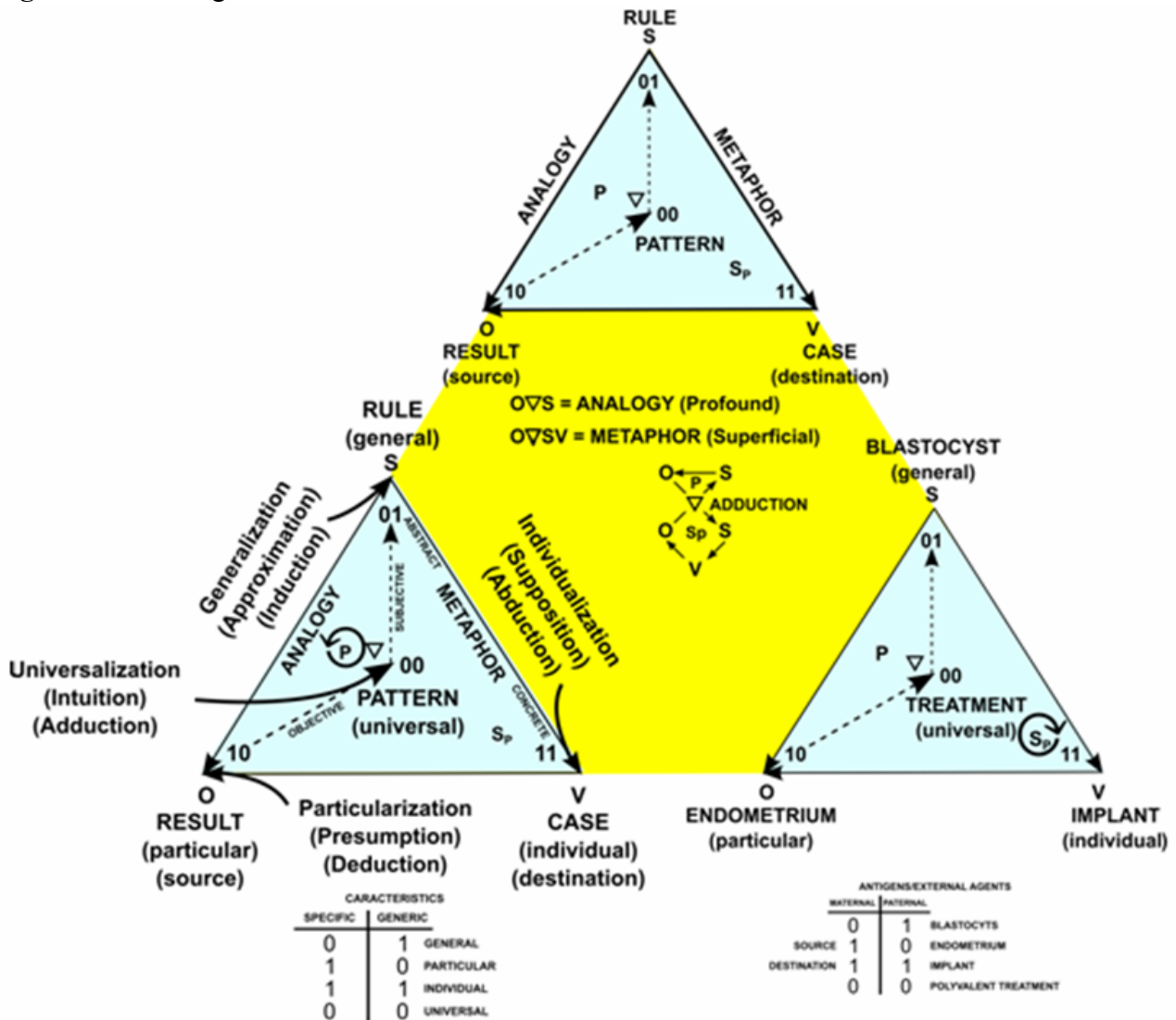
The main purpose of the study was to study the behavior of the endometrium in cases of RIF in ovodonation, having ruled out any intra and extrauterine alterations that could be the cause of RIF or spontaneous abortions.

In order to assure the above, a strict selection of the patients was carried out, in order to ensure a homogeneous population. This selected population is compared against a control group. This group is not chosen by any inductive method, but according to a theoretical model of normal function corroborated by biopsy and bacteriological analysis done to the donors.

‘Isolating’ the endometrium means, that all pathologies involving failed pregnancies have been excluded. In addition, those cases in which, although the transferred material (embryos) was of the first quality, according to international standards, the RIF persisted.

We do not discarded the cases of endometritis (80%) , which after specific treatment and normalization of the altered parameters, were included and submitted to embryo transfer. The following schemes (Figure 2) tell us about the details of the auxiliary method employed in this research.

Fig. 2: Methodological PAU^s



The triangle (yellow) of the scheme composed by triangles at their vertices is intended to determine the methodological integration used in the research analyzed. This generic PAU raises as a rule: "The immune reaction evidenced by an increase in NK (Natural Killers) lymphocytes leads to RIF". Pretreatment results show an increase in a leukocyte sub-population. The case tells us that these cells can be NK_e (endometrial); therefore, failure in the 'implant', having ruled out other causes, depends on the immune reaction produced in the endometrium.

The upper (light blue) triangle speaks of the abductive approach (Salatino, 2009) whose codes emerge from the table of lower left assignments; that is, **rule** (01) belongs to the *general*, the **result** (10) refers to the *particular*, the **case** (11) responds to the *individual*, while the **pattern** (00) is the *universal* implicit in the particular. (Salatino, 2017)

The left (light blue) triangle shows the integration of all the modalities of scientific argumentation that have been taken into account in the research work, whose codes correspond to the same table of assignments above. In addition, it indicates the phenomena of generalization, individualization, particularization and universalization associated with the processes of approximation of induction, hypothesis of abduction, presumption of deduction and intuition of adduction (Salatino's abduction), respectively.

Pierce's abduction tells us about the separation between the known and the unknown. The adduction of Salatino refers to the approximation, until to the simultaneity of these two aspects in a fact, a phenomenon or any process.

Finally, the lower right (light blue) triangle presents the final model used in the research, which seeks a projection of praxis over theory through successive approximations. The table of assignments based on the antigenic contribution of the parents, individualizes with a code the elements that participate in this model: the blastocyst (01) the *general* that depends on the father, the endometrium (10) the *particular* that depends on the mother, the implant (11) the *individual* dependent on both parents and the *universal* (00) that does not depend on any of them, but on the intervening physician. (Ibid, p. 262)

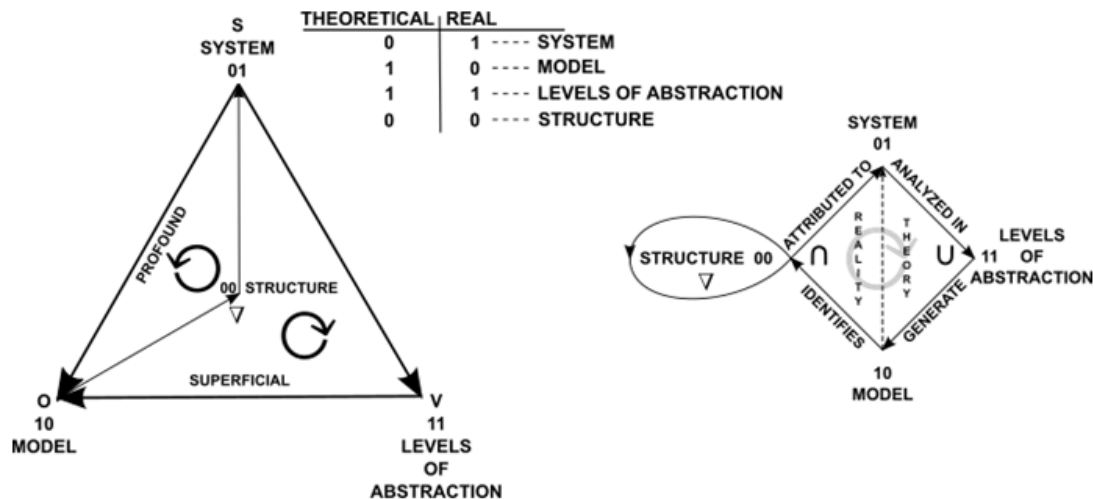
4. FINDINGS & DISCUSSION

The scheme discussed above, in addition to providing methodological aspects, serves as a 'tool' to 'find the hypothesis' that we seek; that is, the treatment that corrects the alterations. After the treatment, it is used again to make empirical findings (the achievement of pregnancies and live births) that fully justify this form of scientific argument. When we talk about hypotheses, we are referring to what guided us to establish a treatment that corrected the endometrial alterations.

Obviously, the contribution of the auxiliary method employed in this work is only epistemological. Its sole purpose is to approach objective reality (implantatory failure) through a set of known variables in order to investigate the existence of some unknown or hidden variable that may be responsible for the results. (Salatino, 2017, p. 273)

As a consequence of this type of analysis of a system, a model can be obtained that takes into account certain levels of abstraction according to the purpose of the studied system. (Floridi, 2008) Strictly following the scheme proposed by Floridi, is elaborated an PAU (Salatino, 2017) according to the disposition of the fundamental elements suggested by TL. (Fig. 3).

Fig. 3: PAU level of abstraction



As shown in Figure 3, a system analyzed according to different levels of abstraction, generates a model (based on a certain theory). The implementation of the model allows identify a structure, which if the empirical evidence corroborates, can be assigned to the system under study. This model, in this work, is proposed in Figure 2.

The study of Tersoglio & Salatino et al. (2015) guided by the previous elaboration showed, among other things, that the multivalent treatment established in the live birth group significantly decreased the amount of lymphocytes and NKe in the controls. In this way, it was possible to demonstrate the reversibility of the histological changes, both ultrasound and immunological by means of an

appropriate treatment in the RIF group, being able to modify the immunological state of the endometrium and thus obtain a live births rate similar to normal.

5. CONCLUSION

The findings in the above-mentioned work demonstrated the reversibility of endometrial histologic changes, both in the ultrasound and immunological studies in a group with RIF that underwent polyvalent treatment. Such treatment was able to modify the immunology and endometrial histology to obtain a significant live births rate.

The previous results were doubly corroborated, on the one hand, from the statistical methods usually used in these studies (op. cit.), and on the other hand, by the ‘isolation’ of the object of study that was made possible by invoking the methodological principles provided by the Transcursive Logic (TL).

It is important to emphasize that this research was the first of its kind, and where the method suggested by the TL was applied. This indirectly confirms that this methodology, originally applied in linguistics, constitutes a legitimate scientific method for dealing with humanistic subjects or those fields of study that belong to the social sciences, as well as to assist the hypothetic-deductive method proper to the natural sciences.

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