A "thought collective" around the idiotype network theory

Review of "The network collective: Rise and fall of a scientific paradigm"

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At a time when biology is dominated by reductionist approaches, it becomes more difficult to look at diverse biological phenomena from a cohesive and global perspective. The field of immunology is no exception, an integrative theory not having been put forward since the development of the idiotype network theory (INT) [1], initially proposed in 1974 by the Nobel Prize-winning immunologist Niels Jerne. The INT was based on the finding that the variable region of each immunoglobulin molecule has a unique determinant, or idiotype, discovered independently by Jacques Oudin of the Pasteur Institute and Henry Kunkel of The Rockefeller University. This finding means that an antibody recognizes an antigenic epitope by means of the antigen-combining site, the paratope, and, at the same time, the idiotype serves as an epitope that is recognized by another antibody. From this scientific fact, Jerne ingeniously formulated the INT, which states that the immune system is composed of a network of antibodies that is interconnected by the binding of the idiotype of one antibody with the paratope of a second antibody, whose idiotype is recognized by yet another antibody, and so on. Thus, in this theory, the immune system is conceived as a self-sufficient, self-referential, and closed system such that the entry of an antigen not only stimulates antigen specific cells but also affects all the cells interconnected with the network formed by the idiotype-paratope interaction. Jerne's visionary hypothesis attracted many brilliant scientists at the time, presumably because it not only explains the raison d'être of the antibody, but it also concerns the regulation of T cells and their products which might lead to a unified theory of the immune system. However, even with the intensive work that spanned from 1975 to 1990, it was impossible to substantiate the INT with experimental data. As a result, the INT is now regarded as a fictional notion in immunology.

Almost all scientists naturally wonder as they reach the end of their careers whether their work contributed in any way to their respective fields and succeeded in establishing scientific knowledge. If you found out that the basis of your work was nothing but a fictitious theory, how would you react to it? As described in "Autobiographical Note", the first chapter of his book, Klaus Eichmann, an accomplished immunologist and a central figure in the German academic system, asked himself the same question. Having been in the middle of the Jerne circle, Eichmann wanted to know above all why so many highly intelligent scientists commit the same errors and draw the same false conclusions. In the process of investigating the theoretical and philosophical aspects of science, he came across the field of epistemology or the study of knowledge, and subsequently learned of the work, *Genesis and Development of a Scientific Fact*, originally published in 1935 by Ludwik Fleck, a Polish medical doctor with a philosophical mind [2]. The analysis by Fleck on the development of Wasserman's reaction for the diagnosis of syphilis demonstrates that the acquisition of knowledge is based on scientific and medical grounds, but that this process is also modified by political and logistic conditions. In other words, scientific knowledge is produced by the endeavors

of human beings called scientists whose activities are influenced, consciously or unconsciously, by their social environments. From this study, Fleck developed important concepts, namely, the ''thought style'' (Denkstyl) and the ''thought collective'' (Denkkollectiv). The thought style implies a way of thinking in which empirical facts are constrained by both non-empirical traditions and subjective fictions of mind. The thought style is shared by a group of individuals, called the thought collective, who form an often-closed community in a given discipline. As American philosopher of science Thomas Kuhn acknowledges, this book was inspirational to his own book, *The Structure of Scientific Revolutions*. Eichmann himself was so struck by the similarity between the story of the INT and the history of Wassermann's reaction analyzed by Fleck that he decided to use one of Fleck's concepts for the title of his book, *The Network Collective: Rise and Fall of a Scientific Paradigm*, as an homage to Fleck's pioneering work.

This book consists of three parts. In part 1, entitled ''Scientific Knowledge, Delusive or Deductive'', Eichmann introduces basic concepts of the philosophy of science from the resources that he accumulated after his retirement as the director of the Max-Planck Institute for Immunobiology and Epigenetics in Freiburg, Germany. He wrote this book to his fellow scientists who, according to him, most likely know only two philosophers of science, namely Karl Popper for his work on falsifiability and Thomas Kuhn for his concept of the ''paradigm (shift)''. In the first five chapters he explains these theories and other basic ideas such as realism, positivism, and constructivism, together with a brief history of the philosophy of science. These analyses with little metaphysical musings should help many scientists understand what is going on in the field of the philosophy of science.

In part 2, ''Origins, Rise, and Fall of the Network Paradigm'', he details the scientific saga of the INT, firstly by summarizing the history of immunology and immunological theories and then by analyzing scientific developments in related fields, such as neuroscience and cybernetics, that influenced the formulation of the INT. This is important in light of Fleck's original observation that elements from distinct fields (or thought styles) can be incorporated into a new thought style, which becomes a driving force of scientific developments, but may also lead to an erroneous paradigm. What actually happened in the thought collective of the INT? Because of the charismatic character of Jerne, people in the network collective gradually came to think that the INT must be true and negative results were not discussed or interpreted from different perspectives but discarded as meaningless because of technical or other problems. In the face of unexpected or incompatible results in deductive approaches, it is the hypothesis, not the result, which has to be modified and reformulated. The principle, however, was neglected in the network collective. When the investigations were expanded to the T-cell field, problems in experimental materials, including polyclonal antibodies and congenic mice, were complicated by difficulties in interpretation and data processing. In the end, the INT turned out to be a fictional notion and disappeared from the scene of immunology.

The last chapter of part 2, ''Hindsight: Personal Interviews'', is devoted to interviews with 11 scientists: Constantin Bona, Pierre André Cazenave, Antonio Coutinho, Ron Germain, Heinz Köhler, William Paul, Klaus Rajewsky, David Sachs, Eli Sercarz, Jacques Urbain, and Hans Wigzell. To obtain well-considered and comparable information, the author sent out 15 carefully chosen questions before interviewing them, either by telephone or face-to-face. The questions include the original attitude toward the INT; the present view on the former controversies on the nature of T-cell receptor, suppressor T cells, and soluble T-cell factors; the reason for the disappearance of the INT; the present evaluation of the INT; and the possibility of new paradigms in immunology, among others. Because of this meticulous preparation, the entire chapter is studded with fascinating reflections and unexpected but important historical information.

It was an exciting read, but what struck me personally is the comment made by André Cazenave of the Pasteur Institute. He stated in a slightly sentimental way:

Independently of the idiotype network, I think it was a time of discussion between people, those working on idiotypic network, but also with people outside of the field or even against the network, just think of Mel Cohn. I think these were very interesting interactions among scientists. This is no more the case.

He further stated in a strong anti-reductionist manner:

At the present time we see a very reductionist approach. Most people are working on signaling, this is interesting, you have to know the signal chains, but you cannot explain how the immune system works... Signaling is important for cell biology but not for how the immune system works as a system, and a system connected with others, which is one of the most important fields in immunology at the present time... There is nobody now who has a larger view on regulation. This is the case in basic immunology, and even more so if we move to immunophysiopathology.

Most of the scientists interviewed in this book agree that at present, there is no comparable paradigm that explains the immunological phenomena in an integrative manner. Is it necessary to search for a unified theory in immunology? And is it feasible to establish one in a field as diverse as immunology? From a practical point of view, it is possible to develop a therapeutic method without a unified theory. However, the real question is whether or not we are satisfied with a situation in which we do not have precise ideas as to what immunity is, or how the immune system functions as a system.

Finally in part 3, ''Science Between Fact and Fiction'', Eichmann reflects, from the philosophical and logical standpoint, on scientific activities and on how scientific knowledge is generated. His view is that science in itself is a fictional activity that uses the imagination of scientists. Only a few fictions become robust knowledge, as evidenced by the fact that among at least 15 theories of antibody formation and specificity proposed in the 1950s, the clonal selection theory of Frank Macfarlane Burnet is the sole survivor of the paradigmatic theory in immunology. There is nothing wrong with

interpreting the data by using scientists' imagination because that is the very essence of science. As Eichmann points out, the real problem is that few scientists are conscious of the fictional nature of their concepts. In this respect, it becomes a prerequisite for any scientist to grasp the basics of what constitutes science in light of historical and philosophical considerations. *The Network Collective: Rise and Fall of a Scientific Paradigm*, a product of Eichmann's extensive and incisive efforts to come to terms with his academic life, gives us abundant first-rate information to reconstitute the recent controversial history of immunology and to reflect upon scientific activities and their pitfalls. This is one of the reasons why this book serves as a good guide for scientists at any level. Furthermore, it may stimulate the generation of imaginative hypotheses with the potential to become robust knowledge in biology.

References

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2. **Fleck L.** 1979. Genesis and Development of a Scientific Fact. Chicago, USA: University of Chicago Press.