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What history tells us XXIV. The attempt of Nikolai Koltzoff (Koltsov) to link genetics, embryology and physical chemistry

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1. Introduction

Nikolai Koltzoff (1872–1940) is mentioned in the historiography of molecular biology as the first to consider a chromosome as 'a giant molecule' (in this article, I have opted for the spelling 'Koltzoff', which Koltzoff himself chose in his publications in French and English). This contribution was first acknowledged by John Haldane in 1945, in his comment in *Nature* on the recently published book of Erwin Schrödinger *What Is Life?* (Haldane 1945; Koltzoff 1928). Robert Olby added one more contribution of Koltzoff: his demonstration of the immense diversity of structures generated by the replacement of residues along a long macromolecular chain – a process he ambiguously named 'isomerism' (Koltzoff 1939). Translating into the informational language adopted by molecular biologists after the Second World War, this means that such long molecules can be the carriers of information: information is contained in the nature of the residues present at each position along the molecule. This anticipates the sequence hypothesis proposed by Francis Crick in 1957 according to which 'the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and that this sequence is a (simple) code for the amino acid sequence of a particular protein' (Koltzoff 1934; Crick 1958; Olby 1974). Conrad Waddington described his work as one of the early European contributions to molecular biology (Waddington 1969). However, this contribution appears limited, and is not mentioned, for instance, in the general description of the rise of molecular biology provided by Horace Judson (Judson 1979).

Koltzoff is also known for his work in cell biology, his careful description of the structure of the giant chromosomes of diptera (Koltzoff 1934), but also for his early description of neurofibrils (Koltzoff 1906, 1912), and his emphasis on the importance of the cell-skeleton at a time when it was barely visible under the light microscope available those days.

Koltzoff was an excellent science manager at the head of the Institute of Experimental Biology in Moscow, which he created in 1917. He succeeded in maintaining this institute at the top international level in a difficult political context.

He is also famous for his head-on opposition to Lysenko in the years 1936–1939, which prevented him from being elected as a full member of the Academy of Science, and led to his dismissal as head of his institute in April 1939 (Birstein 2001; Roll-Hansen 2005). This was not the first time that Koltzoff had had to face political whirlwinds. In 1906 he resigned from his academic position, and in 1920, three years after the Revolution, he was sent for trial, and barely escaped a death sentence. After his dismissal, Koltzoff's scientific reputation saved him from a worse fate, and he died one year later in 1940. Koltzoff's wife committed suicide the night he died. His younger colleague Nikolai Vavilov paid the ultimate price for his opposition to Lysenko, and died in 1943 after three years in prison.

2. Two little-known books

In addition to his scientific articles, Koltzoff published two small (60-page) books in French in the prestigious collection of the publisher Hermann under the general title 'Genetics and the Problem of Evolution' (Koltzoff 1935, 1939). The two books

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are presented as original, although it is clear that parts of them were already present in publications in Russian. The first was published in 1935 with the title ‘Developmental Physiology and Genetics’; the second, published in 1939, was devoted to ‘Hereditary Molecules’. This small publishing house, Hermann, was ideally located, close to the main building of the University of Paris, La Sorbonne. In its collection called ‘Scientific and Industrial Activities’, it had succeeded in attracting some of the most famous French and international scientists such as the biologists Jules Bordet, Victor Henri and Jacques Monod, the physicists Louis de Broglie, Léon Brillouin, Pierre Curie, Albert Einstein and Paul Langevin, the physical chemist Jean Perrin, the mathematicians Elie Cartan, Norbert Wiener and Vito Volterra, etc. The fact that Koltzoff contributed to this collection shows that his work and ideas were acknowledged as important.

These two books have been neglected by historians, probably because they were published in French, and not translated into English. Such books are particularly important for a historian. They contain information that cannot be found in scientific articles, where space is limited and the style tightly controlled. In such books addressed to a large public, scientists do not hesitate to propose hypothetical relations between different fields or domains, and to explain more explicitly the ideas on which the models and approaches are based. These two books do provide interesting clues to the conceptions of biologists in the 1930s, and to the confusion of hypotheses, models and observations from which molecular biology emerged in the following years. They also shed interesting light on Koltzoff himself, his ideas and contributions, and the political context in which he worked.

3. Koltzoff’s opposition to Lysenko

Koltzoff’s two little books in French were written at a crucial time in the history of Soviet science. Despite this, he makes no direct allusion to the political situation, but the way he deploys his arguments (in particular those of the 1939 book) constitutes both a plea for genetics and an answer to Lysenko. Koltzoff begins his second book with a personal reminiscence of the first scientific congress he attended in Moscow 45 years earlier: the congress at which he gave his first scientific talk. Lyev Nikolayevich Tolstoy came to this congress. Koltzoff recalls the position the figure of Tolstoy had at that time – for himself as well as for other congress participants – but also what Tolstoy had previously said about the useless efforts of biologists to describe ‘the details of the details’ and their limited contribution to the progress of agriculture. In the last sentence of his book, Koltzoff returns to this memory and claims that the development of biology during the intervening 45 years had shown that Tolstoy was totally wrong: the increasingly precise descriptions that have been obtained opened new avenues for applications (see later).

Tolstoy’s criticisms of biology and biologists were not so different from those of Lysenko – biologists wander among details and forget to look for applications of the knowledge that they have acquired, and Koltzoff’s reminiscence was a very smart way of underlining their fallacies at a time when the idealism of Tolstoy was being criticized by the Communist Party. It was also a way to reiterate the continuity between Russian science and science as it developed in the Soviet Union.

The first part of the book is a presentation of the main recent results of genetics, and of the huge contributions of Morgan’s school. Koltzoff shows how these results were rapidly reproduced and extended in the Moscow Institute. In contrast to the opposition extolled by Lysenko and his supporters between a proletarian and a bourgeois science, he insists on the rapid circulation of ideas and techniques between different genetics laboratories. He specifically emphasizes the practical results recently obtained thanks to the new science of genetics. By using complex genetic methods developed by the American labs, Nikolai Doubinin was able to obtain in the Moscow Institute what would probably soon be a new species of *Drosophila*, with an altered number of chromosomes. Using the recent observations showing that treatment with colchicine generates polyploidy and more vigorous organisms, the Russian researchers were also able to obtain new and more vigorous plants. Therefore, genetics was able to provide tools to improve crops as efficient as the environmental treatments praised by Lysenko.

Returning at the end of the book to the congress he had attended 45 years before, Koltzoff considers the recent successful developments of biology as the synthesis of conceptions which at that time had seemed to be in conflict. The evolution of biological knowledge has therefore followed a dialectical mode of transformation. The same is true for embryology: a synthesis of the two opposing conceptions which had dominated the field – epigenesis and preformation – was now underway. In this way, Koltzoff paid a discreet but obvious tribute to the official philosophy of Marxism.

An interesting aspect of the 1935 and 1939 books is the total absence of references to eugenics. This contrasts sharply with the place eugenics had in Koltzoff’s 1924 description in *Science* of the work being pursued at the Institute of Experimental Biology. Taking into account the drastic eugenic programme that had been developed in Germany in the previous years, supporters of Lysenko lumped together genetics, eugenics and the fascist politics of Germany. Having been favourable to eugenics was the main criticism levelled at Koltzoff in the 1936 debate.

4. Hereditary molecules

As mentioned previously, the description of chromosomes as molecules of heredity is considered Koltzoff’s most significant contribution to the rise of modern biology. 'Hereditary Molecules' is the title of his French publication in 1939. But Koltzoff went further, and figured out a precise structure for the chromosome. The latter is a long polypeptide chain on which are branched in a complex way amino acids as well as other kinds of molecules such as hormones and nucleotides. Koltzoff endorses the idea of Dorothy Wrinch (Wrinch 1936) that the link between amino acids is not limited to the peptide bond but includes principal and lateral valencies, which explains the complex structure of the chromosome.

Although nucleotides can be branched on this complex network of amino acids, Koltzoff also adopts the point of view of Levene that they are organized in monotonous tetranucleotides, and gives them a limited structural and energetic role (Olby 1974). One of the most original views of Koltzoff – at a time when chromosomes were considered structures of control more or less isolated from the cell – is that chromosomes in his model interact directly with the cell cytoplasm, the nuclear membrane being disrupted at each cell division. Chromosomes can both adsorb and release molecules that are attached to them. The master role of chromosomes comes from their capacity to self-replicate, a process compared by Koltzoff to crystallization. Koltzoff introduced the expression 'omnis molecula ex molecula', based on the famous expression of Rudolf Virchow 'omnis cellula e cellula' (every cell from a cell), in order to emphasize this self-replicating capacity of macromolecules (Koltzoff 1934). This capacity is shared by all the molecules forming the chromosomes: amino acids, as well as steroid hormones and nucleotides. A molecule cannot be synthesized without the presence of a pre-existing copy of it within the cell.

Therefore, the chromosomes are the central place in the cell where the complex molecular and macromolecular structures are reproduced by a process analogous to crystallization: all the molecules and macromolecules that an organism is able to synthesize have to be a part of the chromosomes.

5. Linking embryology, genetics and physical chemistry

To give a precise structure of chromosomes was audacious. It was the most spectacular part of the general project of Koltzoff aimed at reconciling the physicochemical approach of scientists like Jacques Loeb and the embryological descriptions made since the end of the nineteenth century, which culminated in the experiments of Hans Spemann in the first decades of the twentieth century.

The publication of Koltzoff can be compared with *Embryology and Genetics* published by Thomas Morgan in 1934 (Morgan 1934). The absence of real connections between the two fields in Morgan's book has been already underlined (Allen 1978). It contrasted with the German style of genetics, in which genetics and embryology were closely linked (Harwood 1993). Obviously, Koltzoff was close to the German school of genetics. But he went further, trying to relate genetics and embryology through the physico-chemical conceptions of his time. The project appears quite clearly in the 1935 publication. Despite the tribute given by Koltzoff himself to Hermann Staudinger and the concept of the macromolecule, his conceptions remain close to those of colloidologists who emphasized the importance of physico-chemical forces in cell functioning. Two models were recurrently used by Koltzoff to explain the transformations occurring in development. The first was the capacity of cellular constituents to remain soluble or to organize themselves into insoluble structures. This hydrosol-hydrogel transition would be responsible for the formation of the cell-skeleton, the importance of which is emphasized by Koltzoff. Every visible structure in the cell, such as a chromosome, results from the formation of a specific cytoskeleton. The second category of mechanisms resulted from the existence of a force field. This force field drives development, which can be described as the result of the progressive complexification of an initially simple force field. This force field is first 'electrical', which explains why Koltzoff calls intracellular movements during early development 'cataphoretic'. This is also probably why Koltzoff tried to explain the complex behaviour of chromosomes by the existence of opposite electrical charges on them (Koltzoff and Schra-der 1933). But the force field has additional components. It is also mechanical, capillary, diffusional and gravitational. It can result from chemical or temperature gradients. This diversity of forces acting during development explains its complexity: there is no need to appeal, as Hans Driesch did, to a vitalistic principle, nor to contingency, which, for Koltzoff, does not play any role in development.

6. Conclusions

Three additional characteristics of Koltzoff's books should be noted. The first is the astonishing return that Koltzoff makes to physics. As we have seen, Koltzoff favours a deterministic view of development, leaving no place for indeterminacy. He considers that lessons are emerging from recent work in biology, which might be useful for physicists. The latter have emphasized the existence of a fundamental indeterminacy in the physical world. For instance, disintegration of atoms obeys a strict law, but precisely which atoms will disintegrate in the next few seconds or minutes cannot be determined. Koltzoff suggests that we might have access to this information if we are better acquainted with the exact environment of each atom; in the same way as biologists have learnt to anticipate the transformations of cells during development from a precise knowledge of their micro-environment. This was also a way for Koltzoff to present himself as a true Marxist, reluctant to leave a role for contingency within the physical world.

The second original view of Koltzoff is his emphasis on the fact that natural selection acts not only on adult organisms but on all the cycles of development. Such a statement is interesting at the very time that the Modern Synthesis was progressively being shaped, excluding development from the core of evolutionary biology. It sounds like the recent statements of the supporters of Developmental Systems Theory (Oyama *et al.* 2001).

The last observation is more intriguing. When he describes the early phase of embryonic development, Koltzoff uses the word 'epigenetic' to describe the formation of axes in the egg, and the independence of this process from the nuclear chromosomal complex: 'There are reasons to believe that the formation of axes in the egg is an epigenetic phenomenon, independent from the chromosomal complex contained within the nucleus, and that it is determined by the position of the germ cell between the other cells and the tissues of the maternal organism' (Koltzoff 1935). Somehow, Koltzoff initiates this sliding from epigenesis to epigenetics, which will be completed by Waddington. As far as I know, this early use of the word 'epigenetic' has not been noticed by historians and philosophers, who recurrently consider Waddington as the inventor of the word (van Speybroeck 2002; Jablonka and Lamb 2002). It is true that in his first publication on epigenetics, Waddington presents himself as the creator of the word, the result of the marriage between epigenesis and genetics (Waddington 1942). Waddington knew the contributions of Koltzoff; as we have seen, he describes him as one of the European founders of molecular biology (Waddington 1969). He is the only one to refer directly to the French books of Koltzoff, even if he refers to the 1939 book and not the 1935 book in which the word epigenetic was introduced. The hypothesis that Waddington borrowed the expression 'epigenetic' from Koltzoff nevertheless remains to be proved.

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