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# The Other Legacy of Antonie Van Leeuwenhoek: The Polyamines

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## Editorial

Antonie van Leeuwenhoek (1632-1723) left us two legacies; the first is the microscope and the second, the discovering of polyamines in the human semen.

## The Microscope

Antonie van Leeuwenhoek (1632–1723) is the somewhat improbable father of microbiology. A moderately educated owner of a textile business, he learned how to make his own unique microscopes which offered unparalleled magnification. Using these microscopes he made a number of crucially important scientific discoveries, including single-celled animals and plants (In 1674, aged 41), bacteria (1676, this type of organism would not be observed again by any other scientist for over 100 years), and spermatozoa (1677) [1].

Today, it is known that just the human mouth provides a habitat for approximately 700 species of bacteria [2].

On the other hand, the human colon microbiota form one of the densest bacterial ecosystem, with 100 trillion microorganisms which have beneficial health effects such as aiding digestion, resisting pathogen invasion, and producing useful metabolites, but dysbiotic bacterial ecosystems or dysregulated host immunity can stimulate inflammatory response that lead to disease. The composition of microbial population have been shown to be significantly influenced by diet, and these changes are likely to be causally related to several diseases including inflammatory bowel disease, arthritis, allergies, cancers, Alzheimer's disease, obesity, cardiovascular disease and type 2 diabetes mellitus [3].

Some bacteria from oral and gut microbiota have never been isolated.

## Discovery of Polyamines

Polyamines are a group of small molecules whose characteristic is to possess two or more amino groups in their structure. Although several molecules with these characteristics exist in nature, three of them have been the most studied, since there is a close relationship in their biosynthesis and

interconversion in the organism. These molecules are putrescine ( $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$ ), spermidine ( $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$ ) and spermine ( $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$ ). Here is a brief history of their discovery [4].

In 1678, Leeuwenhoek discovered the presence of crystals in human semen. In 1791, Nicolas Vauquelin rediscovered these crystals and demonstrated their relative insolubility in water and ethanol, concluding that they were phosphate salts of an inorganic cation, probably of calcium. Many researchers discovered the crystals that are deposited in the semen; However the nature of this crystallized substance was clearly identified until a century later. In 1853, Charcot, published a paper on the crystallization of spermine phosphate. In 1865 the crystals were described again by Boettcher, who assumed that the substance of which they were formed was a protein, which he called spermatine. Schreiner, in 1878, is credited with the discovery that crystals are phosphate salts of a simple basic organic compound. In 1888, Landenburg and Abel, gave the name of spermine to this organic base, being found in particularly high amounts in human semen (25 mM). Finally in 1926, Otto Rosenheim determined the correct chemical structure of spermine, then synthesizing another base identified as spermidine phosphate. After elucidating its structure the spermidine was isolated from animal organs, microorganisms and plants, resulting in a universal polyamine. The discovery of putrescine and cadaverine is attributed to Brieger's work in 1885, who isolated these bases as double salts of heavy metals from animal tissue. Putrescine, spermidine and spermine are the most studied group of polyamines, although there are other amines that have been detected in several biological systems. The latter besides being found as free bases, can exist conjugated to carbohydrates, steroids, phospholipids, peptides, nucleic acids, also as structural units of numerous alkaloids.

Polyamines are widely distributed in biological systems, although the relative concentrations of putrescine, spermidine and spermine vary markedly in different cell types.

## Biosynthesis of Polyamines

In mammals, biosynthesis of polyamines is carried out from ornithine, therefore, the route leading to the formation of

putrescine is through the enzyme ornithine decarboxylase (ODC). The ornithine available for this reaction comes from plasma and can be formed inside cells by the action of arginase, an enzyme that is part of the urea cycle, which occurs mainly in the liver, but that is also present in the kidney, small intestine and in the brain (arginase is also present in extrahepatic tissues apart of the urea cycle). Spermidine and spermine are formed from putrescine and involve other enzymes; S-adenosylmethionine decarboxylase (SAMDC), and spermidine and spermine synthases, respectively, which incorporate propylamine groups derived from methionine in each case. ODC activity can be elevated several times in response to various trophic stimuli such as drugs, tissue regeneration, growth factors and hormones. Polyamine oxidase is another enzyme involved in polyamine metabolism. Activity of these enzymes have been demonstrated in human spermatozoa [5].

## Polyamines and $\beta$ -cell Function

The pancreas is the gland with the highest concentration of polyamines produced after the prostate gland. Several decades ago arginine was shown to be one of the most potent insulin secretagogue. Subsequently, polyamines, arginine-derived molecules, were shown to increase in pancreatic islets when the proliferation of cells is induced by glucose, growth hormone or platelet-derived growth factor plus insulin-like growth factor. In our laboratory we have observed that administration of arginine causes an increase in the concentration of putrescine, which has been associated with recovery of pancreatic function in rats with chemically induced diabetes.

These experimental evidences have led to study the possible regeneration of pancreatic islets by polyamines, which are known to promote the processes of replication, transcription and translation, and as a consequence cell division, proliferation and differentiation. The morphological changes in the pancreatic islets induced by arginine and polyamines that allow understanding the recovery of biochemically observed endocrine function are being studied by techniques of immunohistochemistry, optical microscopy and electron microscopy by several researches.

## Other Beneficial Actions of Polyamines in Hyperglycemia Conditions

Arginine and polyamines have also shown beneficial effects not only in the regulation of hyperglycemia and dyslipidemia in experimental diabetes, but also in the prevention of glycation of hemoglobin, lipoperoxidation and embryotoxicity, in addition to the excellent antiaggregating effect that has been observed in rat platelets, in platelets of rabbit with induced atherosclerosis, and in human platelets. Recently the inhibition of LDL oxidation of type 2 diabetic patients and their capture by macrophages was also demonstrated, with spermine being the polyamine with the most potent inhibitory effect, which has been associated with the polycationic properties. Intracellular de novo synthesis and concentrations of polyamines in cells and tissues, especially those of spermine and spermidine, decrease with ageing. In uncontrolled type 2 diabetics a premature ageing is presented. Lipid peroxidation in vivo has been identified as a basic deteriorative reaction in cellular mechanisms of the ageing.

In conclusion, many researchers are currently conducting studies on the biological role of polyamines in health and disease. Particularly in diabetes the results are encouraging. Thanks to Leuwenhoeck's observations of the crystallization of spermine, a real industry has now developed on the study of the biological role of polyamines.

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