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Opinion

Agricultural, Food and Environmental Microbiology at the University of Padova: An Evolutionary Journey from Lag Phase to Exponentiality

Lorenzo Favaro *, Marina Basaglia, Viviana Corich, Alessio Giacomini, Sergio Casella and Andrea Squartini

Department of Agronomy, Food, Natural Resources, Animals and Environment (DAFNAE), Campus of Agripolis, University of Padova, Viale dell'Università 16, 35020 Legnaro, Italy
* Correspondence: lorenzo.favaro@unipd.it

Abstract: This paper is a microbiological voyage throughout the main discoveries and research activities of scholars who studied or taught in this field at Padova University during its 800-year history. The ancient practice of variolization, the so-called miracle of Legnaro and the pellagra debate, whose observations and investigations were driven at Padova even before microbiology was established as a scientific discipline, along with the modern era research activities in the field of agricultural, environmental and food microbiology, undoubtedly suggest the hallmark and everyday role played by microbes in overwhelmingly global, but profoundly human, adventures.

Keywords: microbiology; discovery-driven and hypothesis-driven science; smallpox virus; *Serratia marcescens*; pellagra; Incrocio Manzoni

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1. How Old Is a Thing: Existence vs. Knowledge

The timeframe allowed for the present special issue is the past eight hundred years, being the period elapsed since the foundation of the University of Padova (Padua) in 1222. When dealing with microbiology in such a retrospective, a first apparent hindrance is faced; since microbes were not known to man until the mid-1600s, at least half of the time available for the present essay could seem already unusable. However, the matter assumes a different nuance when we start to consider that most of what we define as 'knowledge' is simply the updated interpretation of phenomena due to pre-existing, hitherto unknown, causes. In this light, considering that the first of all life forms is credited to have been a bacterium, we can reverse the story and observe that microbiology is the youngest born of biological sciences but the oldest thing in nature's reality.

Studying it made mankind gradually aware that all life forms on earth just evolved from that first prokaryotic cell, and, in this sense, we are ourselves simply among the current progeny of a microbe.

Therefore, when we comment on analyses carried out by scholars who studied or taught at the University of Padova, and whose topics have to do with microbes, some of those observations occurred even before those investigators were aware of the actual causative agents of their subjects, whose nature was yet to be discovered. However, although completely overlooked by common knowledge, one of the first documents witnessing the human consciousness of the presence of extremely small 'beings', invisible by the naked eye, that could enter our bodies through the mouth or nose, dates back to 37 B.C., when Marco Terenzio Varrone hypothesized the occurrence of "*animalia quaedam minuta quae non possunt oculi consequi et per aera intus in corpus per os ac nares perveniunt atque efficiunt difficilis morbos*". Moreover, and appropriately for our purpose here, such piece of knowledge belongs in a treatise about agriculture: *De re rustica*.

An equally challenging issue, and perhaps an even more imbalanced one, is indeed related to the framework suggested by the hosting target journal of this series: Agriculture. In fact, from the formal point of view, the Agriculture College at the University of Padova was established only in 1946, less than one-tenth of the 800 years of history of the entire institution. Yet nonetheless, we find that agricultural experimentation was thought and practiced under other academic branches in Padova, long before a specific degree would be coined. Indeed, as early as in 1762, the first Chair of Agriculture in Europe was constituted at the University of Padova. In 1792, independently from the Botanical Garden, an Agricultural Garden (Orto Agrario) was operative, in which 645 species or varieties of cropped plants were grown to deal with famine prevention, pest fighting and food improvement [1]. In fact, even when not featured in the academic spotlight, agriculture has always been an indispensable know-how ruling human existence and survival since the Neolithic over 10,000 years ago, when most of our ancestors stopped relying on the hunting-gathering primary lifestyle. Indeed, the silent prominence of the microbe's role in billions of years of natural history finds a parallel for the discreet but vital role of agriculture, as the earliest of human choices since the Holocene.

2. Microbiology before Microbes

Vaccination is in modern times recognized as a life-saving preventive measure against infectious diseases. The acceptance of this rationale is undoubtedly facilitated by the notion of precise microbial agents as the aetiological causes of given diseases. Understanding the concept from the scientist's standpoint became easier once the existence of 'invisible' life forms, such as bacteria, had been proposed in 1665 by Robert Hooke who described the fruiting structures of molds, and Antoni van Leeuwenhoek who is credited with the discovery of bacteria in 1676. Microbiology, however, achieved the standard of an official discipline only later when, in the 1870s, inspired also by the Italian priest and biologist Lazzaro Spallanzani [2], Louis Pasteur's germ theory of illness was diffused, followed by the postulates that Robert Koch published in 1890 [3].

However, the earlier concept of a 'mild challenge' to a human subject with small amounts of material taken from a diseased patient, was for a long time held on the verge of a practice between groundless intuition and empirical spirit. In this respect, the official forerunner of vaccination and immunology is popularly indicated as Edward Jenner, who started applying vaccinations against the smallpox virus in England in 1796 [4]. Nevertheless, Sir Francis Galton would later say, "In science, credit goes to the man who convinces the world, not the man to whom the idea first occurs", and this ties to two Venetian scholars who had graduated at the University of Padova, Jacopo Pilarino and Emanuele Timoni. Both successfully experimented in Constantinople the practice of 'variolization', i.e., inoculating a healthy individual with material isolated from the smallpox vesicles of a diseased one. Pilarino carried out the first reported inoculation in 1701. The published method appeared in 1714 [5]. Before that, Timoni, in 1713, wrote to John Woodward, president of the Royal College of Physicians in London, to whom he recommended the method [4]. The popularity in the British Isles of the practice suggested by the two Italians was also fostered by Lady Mary Wortley Montagu, wife of the British ambassador in Constantinople, who insisted on treating her first son and advocated in favour of the introduction of the practice in the United Kingdom. The Royal Family was eventually vaccinated, starting in 1722 with Caroline of Ansbach, wife of King George II [6]. Thus, smallpox vaccination had been used in Europe almost a century earlier than its first application by Edward Jenner. England itself had already tested it three decades before Jenner's birth on the Princess of Wales in person. In addition, in regard to Jenner's adoption of a cow-derived inoculant to treat humans, the first use is reported in 1763 as done by John Fewster, a surgeon and pharmacist in Thornbury, seven miles from Berkeley, which was Jenner's birthplace. Fewster shared his hypothesis that a treatment with cowpox could give protection against the human disease smallpox as well, during a lunch of the local medical society. The gathering was attended, among others, by Daniel Ludlow, a pharmacist from Berkeley who was accompanied by his young apprentice, Edward Jenner [7].

In any event, Pilarino and Timoni, the two physicians that had graduated at the University of Padova did not claim to have been the discoverers of the variolization technique, as they had just contributed to the extension towards the western world using what they had learned themselves in Turkey, where it had been, in turn, introduced from farther Asian origins, being reported as a practice already known in China in the tenth century [8].

The smallpox saga shows that "microbiology before microbes" has been perpetuated seamlessly for over a millennium and that actions can precede understanding and disciplines development when it comes to matters of life and death. This is particularly revealing if we consider that the smallpox agent is a virus, and the discovery of viruses by science occurred only between 1892 and 1898 with the tobacco mosaic virus as the first known case [9].

However, despite all scientific advances, the perception of viruses as threats and the acceptance of vaccination by overall public opinion is still a totally divisive issue. The unexpectedly large share of anti-vaccination positions uncovered by the COVID-19 pandemics has shown how difficult a scientist's job is. This indicates that understanding does not necessarily warrant common-sense actions, while, in particular situations, as we just commented, the opposite could occur. This leads to an apparent paradox. The attitude of anti-vax activists is often in favor of a series of other themes within the non-mainstream choices, among which there is a certain trust in alternative remedies such as homeopathy. Ironically, the principle of vaccination (using a very little amount of the toxic agent to trigger immunity) is conceptually in the very same frame of thought as homeopathy, the difference being the order of magnitude of the dilution process.

3. Food Microbiology in Legnaro Two Centuries before Agripolis

The agricultural and veterinary sciences campus at the University of Padova, named Agripolis, is located within the township of Legnaro, seven kilometres south-east of Padova, where researchers and students moved in the mid-1990s upon the completion of the new departmental buildings beside the experimental farm. Independently from such choice, a peculiar fact is found in the local annals of that town within the 1819 chronicles [10]. At the time the event was referred to as "the miracle of Legnaro" an apparent mystery that attracted a large deal of attention, to be finally: (a) solved by a young pharmacy graduate from the University of Padova, and (b) demonstrated to be a food microbiology case. These two conditions that make the case qualify for the present report are, moreover, crowned by a third: (c) the fact that it occurred right in the place where our Department (DAFNAE) would locate its home nearly two centuries later, giving the whole thing the flavor of predestination.

It was a hot August day during that summer of 1819 when the Pittarello family, landowners and farmers in Legnaro, were gathering for supper but noticed something unusual on the prior dinner's polenta leftovers. This typical cornmeal porridge had become the basis of most northern Italian people's nutrition since the prior century. Scarlet-red, bloody-looking spots were irregularly covering the food. Within a few days, the strange phenomenon also appeared in other homes among the peasants of Legnaro, and the rumors spread quickly. Fearing witchery, the folks called in the parish priest who just said that, up to that moment, the sacred hosts of his church were still white, and brought the case to the Archibishop of Padova. Being the region of Veneto under the Austrian domination, the enquiry also involved the military garrison. In the meantime, the 'crimson polenta syndrome' spread across Padova's southern territory. An official committee appointed by the Austrian governor of the city started to investigate but did not find an explanation. The story was leading the news headlines of the region and stirred the curiosity of a young pharmacy student at the University of Padova, Bartolomeo Bizio. He rented a horse and rode to Legnaro. The patriarch of the Pittarello family, Antonio, was initially very reluctant to cooperate as he had hardly succeeded in sidetracking the Austrian administration committee from the suspect that his home was the focus of origin of the whole story, but Bizio knew how to use an element which would soon turn into an asset for modern applied research: the prospect of business. Explaining that, possibly, a novel type of color for garment dying and other uses could have been extracted and exploited if one would multiply the red spoilage on fresh maize flour, Bizio convinced him and had a sample from which he started his experiments. He was able to reproduce the phenomenon, isolate the agent, characterize its morphology, and he is credited to have been, long before the era of Pasteur and Koch, the first who isolated a bacterium in pure culture on a solid medium. He gave a name to the taxon, *Serratia marcescens*, (dedicated to Serafino Serrati, a benedictine monk of the 18th century who had invented the steamboat), which is currently the standing nomenclature for this member of the *Enterobacteriaceae*. Thus, Bizio still as a graduate student, besides solving the 'Miracle of Legnaro', dispelling superstition and religious fears, had also discovered and validly described a novel bacterial genus and species. The purple stain turned out to be ethanol extractable and Bizio continued working on that and other red pigments, which led him to another of his contributions to science advancement, clarifying the chemical nature of the other famous red pigment, the precious purple dye from the *Murex* mollusks traded by the Phoeniceans since antiquity. Bizio demonstrated that it is the secretion of the intermediate portion of their hypobranchial gland, and that, upon oxidation, different copper-containing compounds are formed, with a palette of different red tints, depending on the producing mollusk taxonomical species [11].

4. When Microbiology Is Not the Point; the Challenge of Hypothesizing the Null

This case has the polenta corn meal again as the topic, which is a leitmotiv for Veneto's identity, but for a completely different and somewhat opposite reason. It also offers an example to introduce an important virtue in a scientist's mind and the consequences of it lack. The quality is being able to renounce the seemingly most intuitive explanation and to put into discussion any possible upstream assumption that could stem from prior knowledge examples. The person is Filippo Lussana, who taught Anatomy and Physiology at the University of Padova, from 1867 to 1889 [12], and the case is the pellagra disease, on whose cause two completely opposite interpretations were at stake. Starting from the 1700s, corn, introduced from central America after Columbus, gradually became the staple food for several European populations, including the Spanish Asturias, Southern France, and the Northern Italian Po valley belt from Milan to Venice [13]. In the rural areas of those places, a novel disease, appearing as severe dermatitis, diarrhea and later dementia, was rapidly hitting farmers and countrymen, reaching devastating proportions for most of the 1800s.

In science, when seeking interpretations, a primary innate mechanism is the causal nexus: "something (existing) is causing the observed phenomenon". This process of reasoning is deeply embedded in human brains as it entailed an evolutionary advantage ("the cracking noise I just heard, could be due to a wild animal which could now appear"). Therefore, when something visible/perceivable happens, our innate tendency is to imagine that the presence of a physical entity has determined that consequence. A much less natural effort of abstraction is necessary to suppose that the *absence* of something would be causing that. This is mostly because that hypothesis stems instead more easily when a phenomenon *does not* happen (a plant does not bear fruits due to the lack of nutrients). Under these premises, many of those who had studied the pellagra case were strongly supporting the hypothesis that corn could have become infected by some intoxicating germ [14]. The main proposer of this view in Italy was Cesare Lombroso, whose more popular studies were those devoted to the theory that criminality was an inherited trait and that criminals could be identified by physical defects, particularly in their skull [15]. On the contrary, Filippo Lussana with Carlo Frua published in Milan in 1856 the result of their research [16], stating that pellagra was not due to the presence of any toxins, but rather the result of a lack of proteinaceous material or other needed forms of nitrogen, in corn flour, and that would manifest in people who had no access to additional nutritional sources to mitigate such deficiencies. Indeed, they had correctly diagnosed the reason for pellagra, which is the low content of available niacin and tryptophan.

Despite these early-provided notions, the prevailing alternative theories persisted quite extensively. Pellagra did later occur in the United States as well, where from 1906 to 1940 more than 3 million people were affected by it, with more than 100,000 deaths, before the clue of missing nutrients could be examined and the truth re-discovered [17].

Interestingly enough, speaking about disregarding opponents' ideas when those are adverse to one's theory, or simply ignoring prior culture, it is known that Native Americans from Mexico and other areas from which corn originates, had already found a simple disease-preventing treatment which is called nixtamalization. It involves soaking the corn grains in alkaline solution as limewater or carbonated water, washing and hulling them. Besides enhancing aroma and flavor, the process almost completely reduces aflatoxins [18]. Moreover, hemicellulose-bound niacin is converted into free niacin, greatly increasing its bioavailability upon consumption, which explains why pellagra was not known among the native American cultures.

Thus, although Lombroso and others such as Carlo Mantegazza (a physiologist and theorist of race superiority in evolution, that was criticized for his massive use of animal vivisection already in the 19th century) were fiercely supportive of the germ-caused pellagra hypothesis, Filippo Lussana stood for the opposite view (no thing is the cause).

The example also teaches that many people tend to interpret things primarily based on what they mostly know. Microbes had started to become examples of causative agents of the most horrible human diseases; leprosy was somewhat similar to pellagra's skin symptoms; the polenta itself was infectable by the red *Serratia marcescens* (which is also an opportunistic pathogen), and hence it was easier to go for the most plausible explanation. In this sense, people such as Lombroso and Mantegazza proved how one could be a victim of what is known as professional deformation. In addition, a person's general attitude can add to this bias. Indeed, Lombroso and Mantegazza were in all their research fields 'inquisitory' types, theorizing people's inferiority or acting hatefully against convicts and caged animals on the experimental side. It could appear natural that, when choosing between two opposite explanations, they would go for the one where there would be a culprit to blame.

Filippo Lussana instead, besides having authored more than two hundred scientific publications on several other topics at the University of Padova, received two gold medals from the Royal Society of Medical Sciences and Natural Sciences in Brussels, and the Royal Academy of Medicine of Belgium. Aside science, he was also a writer, a painter, and a poet.

5. Through the Grapevine; Conegliano, the Oenological School and the Second Campus

There are two basic ways to conduct science: discovery-driven and hypothesis-driven. The former is the situation in which facts can actually precede the scientific approach and even postpone it indefinitely. It occurs when a discovery can be exploited as such within a merely empirical context. If instead one is testing hypotheses, thus planning that knowledge should stem from a question, science is by definition the starting element. To some extent, the former case tends to apply to positive and useful phenomena, whose benefits appear inherent to the observation in itself. Conversely, the urge for hypotheses to explain and possibly revert some occurrences is essential for those phenomena that represent adverse outcomes for our society, such as diseases, harvest-threatening pest outbreaks, and environmental trends to global changes. In other words, scientific knowledge tends to be regarded as crucial for threats but as facultative or less compelling for what is regarded as the beneficial side of things. Such distinction has consequences on the priority-setting mechanisms for research funding and renders studying some topics a hard endeavour.

There are, instead, important examples of human know-how that started off from ancient discoveries and that have been fruitfully applied for amazingly long times before science would start dealing with them and unraveling their origin. We cited agriculture as one of the earliest human technologies, but there are evidences of an even earlier one, whose key players were (unknowingly) once again some microbes: alcoholic fermentation. There is evidence that, before the Neolithic revolution, around 12,000 years ago, the hunters-gatherer types of communities used honey from forest beehives to be mixed with water to obtain hydromel. A food microbiology subject as alcohol fermentation appears to have been the unknown basis of our activities even earlier than agriculture and animal domestication. The subsequent records of human use of all sorts of sugar-containing substrates to produce beer, already in ancient Egypt, and wine, nearly everywhere grapevine cultivation was enabled by climate and soil, are now often part of a proud collective heritage. Nevertheless, viticulture and oenology have been for a long time, and still are, examples of practical and traditional knowledge that could develop within their own technical sectors and tended to do so without the help of academic research. However, in recent times this changed and did so rather rapidly, up to the point that science and winemaking merged profoundly and with evident rewarding benefits. The University of Padova has, since 2001, a second campus in Conegliano, where it has synergistically joined one of the earliest local centers of applied studies in grapevine cropping, cultivar selection and wine production of the Veneto region. This was formerly the Oenological School of Conegliano, established since 1876 by Royal Decree from His Majesty King Vittorio Emanuele II. A degree in Viticulture and Oenology Science and Technology from the University of Padova is now held there and research laboratories with state-of-the-art technology are operative in parallel.

Yet long before that, an early connection had been already established between the School of Conegliano and the academics. This involved one of the most renowned directors of the Oenological School, Prof. Luigi Manzoni, who in 1936 became a lecturer of Plant Pathology at the University of Padova [19]. Manzoni's work was in the plant breeding practice and his grape hybrids originated several different varieties with highly appealing properties, that are currently in use, and known as the Incrocio Manzoni denominations.

6. The Modern Era, 1946–1980

Although, as previously reported, the first Chair of Agriculture was established in 1762 and assigned to the botanist Pietro Arduino, the Agriculture Faculty was established only in 1946 [20]. Since that time, microbiology was taught in the course named Technical and Agricultural Microbiology by Giovanni Luchetti. He graduated in Agricultural Sciences at Pisa University in 1931, and started his career at the same University under the guidance of Renato Perotti, recognized as a pioneer in the concept of microbial endophytes. He first worked as a volunteer assistant in Plant Biology (1931–1934) and then as a fellowship holder in Agricultural Bacteriology and Plant Pathology (1937–1942). His time at the Institute Pasteur (Paris, 1936–1937) had a great impact on his professional life. After the Second World War (and being awarded with the War Merit Cross after his imprisonment in a German Camp from 1943 to 1945), Luchetti moved from Pisa to start teaching at the newly established Agriculture Faculty at Padova University. In the early 1950s, he launched research activities fully novel for Padova University in the field of agricultural, food, and environmental microbiology. He continued his research activities on soil microbiology, mostly on the saline soils surrounding Ferrara, where he lived for many years in a house where he was proudly able to install his own microbiology laboratory. He explored yeast and lactic acid bacteria potentialities in ethanol and cheese-making applications, and he undertook interdisciplinary approaches useful to deepen studies on the soil fatigue mechanisms. In the 1970s, he also started to monitor the fate of surfactants and detergents in soils and rivers, and their effect on plants and microbes of agricultural importance. Interestingly, the research seeds he contributed to sow are now the three main microbiological research fields at Padova University, namely agriculture [21–23], food [24], and environment [25]. Luchetti, retired in 1978, continued his teaching activities at Padova University two more years before his death.

7. The Growth Phase and Its Hereafter

At around the midpoint of the time period between the agricultural sciences college establishment and today, a successional turnover of the people in charge of the agricultural microbiology sector occurred, which can be seen as the beginning of the subsequent cycle. Not unlike the growth curve of a viable microbial culture (and, for us authors, faithful to our own biology model of reference), an increase in numbers occurred as well. In the pioneering (and lag) stage, Giovanni Luchetti had been the sole microbiologist and taught his single course continuously for 34 years. When he passed his relay baton witness, the person who collected it was Marco Nuti, again from the University of Pisa, which for almost the next 10 years ran alone as well but, after that, in 1990 the faculty members of the microbiology group doubled, and a growth trend started that would see a further entry in 1992, one in 1996, (the year in which Marco Nuti moved to the University of Pisa), after which other additions occurred, twice in 2001 and one in 2015, when the group reached six faculty members, whom are the coauthors of this manuscript.

Besides the mention to Marco Nuti as having had the chance and the merit to provide the impulse for turning a viable 'monophyletic germline' into an evolved 'culturable and differentiated colony', it is worth mentioning his contribution to the advancement of the knowledge in agricultural microbiology, which is best exemplified by the seminal paper that he published at the time he was being recruited by the University of Padova. It is a publication in Nature in which he is the first author, and that demonstrated that the genes for nitrogen fixation in the rhizobial symbionts of legumes are not on a chromosome, being instead encoded by large transmissible plasmids [26]. As an example of a different achievement of his, in the context of policy-making, consulting, and EU guidelines implementation, after co-leading a series of international research projects (BAP, Bridge, Impact 1) on the Risk Assessment for the Release of Genetically Modified Microorganisms, he led the first experiment in the field release of genetically modified microorganisms in Italian territory, which took place at the Legnaro experimental farm of the University of Padova in 1994 [27].

In essence, although the octo-centennial of Padova University is about to be celebrated by special issues such as this one, the story is not ending and will continue. The lag phase of our small academic sector shifted to a more logarithmic shape and could be claimed to have reached a positive-sounding, six-fold increase in structured members, and that, at the same time, the number of courses taught in the academic year rose from 1 to 25. In ecology, this would suit the description of a species that shifted from a moderate and quiet K-selection to an overt r-strategy. A feeling which is, at the same time, bringing both pride and challenge, hopefully in balanced amounts, to be lived through the time ahead.

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