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Minireview – Professional Development

The vanishing link between animalcules and disease before the 19th century

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One sentence summary: Even though many 17th and 18th century scientists recognised the association between microorganisms and diseases of plants, animals, and humans, opposition to the idea dominated until the late 19th century.
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Abstract

When Antoni van Leeuwenhoek began his work with microscopes in the late 17th century, western medicine was mostly based on the work of a Roman doctor called Galen (129–199 AD), theological interpretation, superstition, and folk remedies. During modern discussions of Van Leeuwenhoek's work, a common question from listeners is why it took so long for the link between Van Leeuwenhoek's discoveries and infectious disease to be accepted. Published literature, examples of which are discussed here, shows that many researchers, doctors, and others reported the link, even during Van Leeuwenhoek's lifetime. However, it was frequently not taken seriously by the most influential people. The scientific establishment included a faction of the Royal Society of London who called themselves the 'Mechanical Philosophers'. They ridiculed those reporting animalcule-linked infection, dismissing them as 'Contagionists'. The medical establishment also included many influential people with a lot to lose if they changed their established approaches, and many quack doctors. Most religious ministers were strongly orthodox, some even claiming that helping the sick angered God. A major problem, of course, was that technology and biological understanding also lagged far behind. Despite the fact that the use of vaccination was under active discussion in the Royal Society at the time of Van Leeuwenhoek's death and quarantine was in regular use, a possible microbial connection was apparently not considered. It was not until late in the 19th century, that Robert Koch (1843–1910) isolated *Bacillus anthracis*, proved that it caused anthrax, and was believed. This paper follows a lecture given during the online Microbe Forum in June 2021, and illustrates the difficulties of establishing the true link between Van Leeuwenhoek's animalcules and infectious disease in humans, animals, and plants.

Keywords: Leeuwenhoek, animalcules, fake cures, plague, smallpox, microorganisms

Introduction

In the centuries since Antoni van Leeuwenhoek discovered his assorted microorganisms (known as animalcules, worms, little animals, and other terms), people have speculated about how he achieved his results. Some writers have claimed that he must have used special or secret instruments in addition to those he showed visitors, especially in order to see bacteria (Fig. IV in Fig. 1). In recent years, it has been possible to repeat many of his experiments and resolve some disputes (Robertson 2014, 2015, 2019). One question, however, is regularly asked. '*Why did the link between microorganisms and disease have to wait nearly 300 years to be accepted?*' Examination of publications from Van Leeuwenhoek's time show that the link was suggested and accepted by many, even before his death. What happened?

After the withdrawal of the Roman Empire from Europe, standards in science and medicine fell during the so-called 'Dark Ages'. As late as the early 17th century, the primary medical text in Europe and the New World was still that by Claudius Galenus, a Greek–Roman surgeon and author from 1500 years before. One advantage gained by doctors who studied his work was that he described practical investigations including dissections, which were later forbidden by the Christian Church. His book is still in print in different translations, and versions from Van Leeuwenhoek's time (generally in Latin) can be found online.the legend to Fig 1 refers to Van Leeuwenhoek's numbering on the figure.

During the 16th and 17th centuries, scientific research became organised. Universities, scientific academies, and societies were formed. Scientific theories and medical approaches began to be published and discussed. Not long after Antoni van Leeuwenhoek published descriptions of his animalcules (they did not distinguish between protozoa, algae, yeasts, or bacteria; Fig. 1), some members of the Royal Society suggested a link with disease (see below).

The published reactions of the medical and theological fraternities to the outbreaks of disease (generically called plague) running rife during the 17th century provide a summary of attitudes at that time. A selection can be found in Payne's introduction to his publication of William Boghurst's 1665 manuscript about the Black Death in London (Payne 1894). A few examples are shown in Table 1. Some were factual accounts of the progression of the plague, but many authors had opinions about the cause and treatment which they published as facts. Various cures and modes of prevention were suggested. Essentially, everyone had their own opinion, few if any of which had a practical basis.

In 1656, nearly 20 years before Van Leeuwenhoek began writing to the Royal Society, the Jesuit Athanasius Kircher examined

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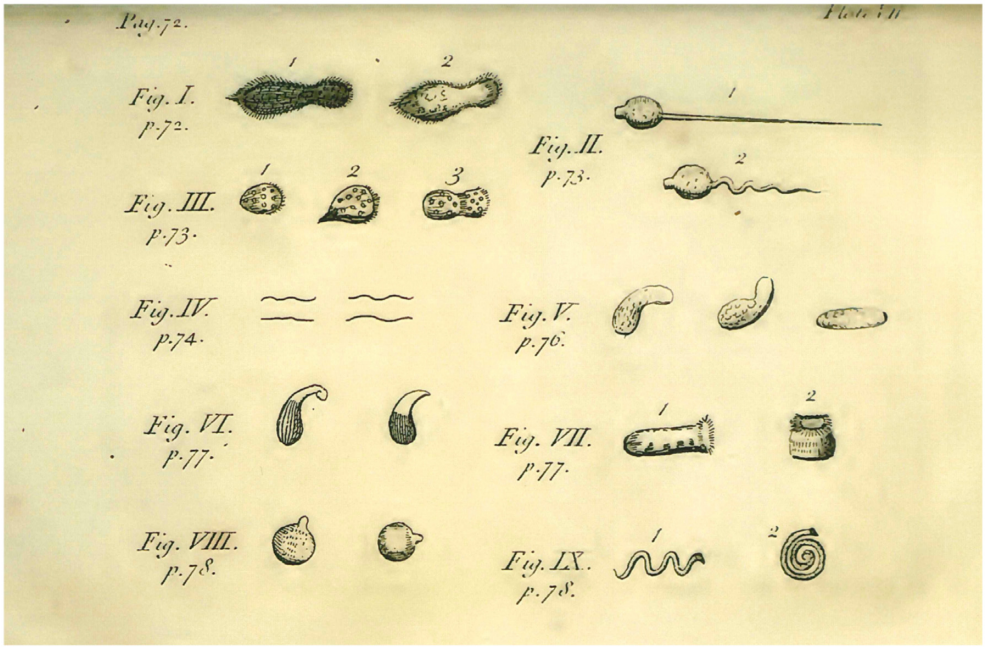


Figure 1. Copy of the drawing that accompanied Van Leeuwenhoek's letter about his pepper water experiment (Van Leeuwenhoek 1676). The original drawing has not survived, but Henry Baker published his version as an exact copy (Baker 1742). Figure IV is regarded as the first published drawing of a bacterium among the various protozoa.

Table 1. Examples of books and pamphlets written and sold in London after the Black Death epidemic of 1665, and listed in the introduction to Boghurst's manuscript (Payne 1894).

Author	Title	Comments (in italics) from Boghurst's manuscript.
Gideon Harvey MD	A Discourse on the Plague	*Forecast that the epidemic portended no great mortality*
Theophilus Garencières, Dr in Physic	A Mite Cast into the Treasury of the City of London, a Discourse on the Plague	*'The plague is one of the easiest diseases in the world to be cured, if it be taken within four hours after the first invasion; otherwayes and for the most part mortal.'*
Thomas Cock	Hygiene, or a Discourse upon Air, with Cautionary Rules for the Preservation of People in this Time of Sickness.	*Contains a strong protest against the practice of shutting up infected houses.*
Richard Kephale	Medela Pestilerdice. Theological Queries concerning" the Plague; also Method for curing that Epidemical Distemper.	*Half the book is theological, half medical, containing a very fair though short account of the symptoms of plague from personal experience*
J.V.	Golgotha, or a Looking-glass for London, shewing the Causes of the present Plagues, with an humble Witness against the Cruel Practice of Shutting up unto Destruction.	*A protest, in most unmeasured language, against the shutting up of infected houses. The writer was not a doctor, but probably a minister*
John Gadbury (the Astrologer)	London's Deliverance Predicted; in a Short Discourse on Plagues in General	*Deals chiefly with astrology, pronounced that October seemed to promise well. (The epidemic spiked at 26,230 deaths in September, in October it was 14,373).*
Theodore Beza Vezelian	A Learned Treatise of the Plague, wherein the Two Questions: Whether it may be Infectious or no; and whether it may be shunned of Christians by going aside are resolved.	*Theological, and intended to comfort the consciences of those who in such terrible epidemics sought safety in flight. He says that those who fail to run away are wicked and provoke God.*
Company of Parish Clerks of London	London's Dreadful Visitation, a Collection of all the Bills of Mortality from Dec. 27, 1664, to Dec. 19, 1665	The only book based entirely on fact, listing death numbers per parish per week, and summarising the cases of death.

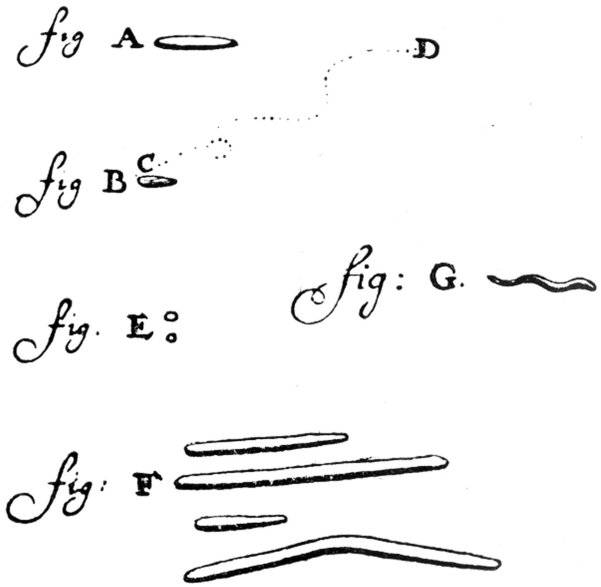


Figure 2. The bacteria observed by Van Leeuwenhoek in scrapings from his own teeth after he did not clean them for a few days (Van Leeuwenhoek 1684). There can have been no doubt in his mind that his animalcules came in a range of sizes and shapes.

blood from plague victims under his simple microscope, and announced that he had seen tiny worms, which were spreading the disease (Kircher 1656). He considered that they were similar to the tiny worms that appeared from dead animals, and their existence supported spontaneous generation. In 1688, Francesco Redi showed that the 'worms' only appeared if the flesh was exposed to flies, and eventually hatched into new flies (Redi 1688). Kircher's microscope only magnified about 32×, and could not have shown bacteria.

The situation was complicated by disputes between researchers with interests in biology and chemistry, and those who claimed that only physics and mathematics gave definitive answers and were, therefore, important. The latter called themselves 'Mechanical Philosophers' and dismissed the others as 'Contagionists'. For convenience, these names for the opposing groups will be retained here.

This paper aims to show how the connection between animalcules and infections of people, animals, and plants was both suggested and declared to be fact by various researchers. As time went on, the belief then faded in the face of opposition from influential scientists, Churchmen, and what is known today as 'fake news'. Other potentially supportive connections were missed.

The contagionists

Van Leeuwenhoek's discoveries of microorganisms (Figs 1 and 2) have been well-documented in many books and reviews (e.g. Dobell 1932, Robertson et al. 2016) as well as his own words (Van Leeuwenhoek 1676). Less than 3 years after his first letter about animalcules in lake water, 'An Observing Person in the Country' (Anon 1677) wrote to the Royal Society to speculate that if the air is also full of little worms, they might be causing 'general infections of men or animals' at certain times of the year. Other observations followed, including from Dr Wincler, Chief Physician of the Prince Palatine, who wrote to Dr Fred Slare FRS (Wincler 1683) that the cattle plague in his area was due to some 'volatile insect' rather than evil incantations, the arrangement of the planets or a 'blind putrefaction'. He wished that Mr van Leeuwenhoeck (sic) had been present at the dissection of the animals to find anything. Note that microorganisms were often collectively called 'insects' as well as 'little animals' and 'animalcules', among other terms.

Many other similar reports were published, including those of Dr Benjamin Marten in his book '*A New Theory of Consumptions*' (Marten 1720, Doetch 1978):

> 'The original and essential cause, then, which some content themselves to call a vicious Deposition of the Juices, others a salt Acrimony, others a strange Ferment, others a Malignant Humour (all which seem to me dark and unintelligible) may possibly be some certain species of a*nimalcula* or wonderfully minute living creatures, that, by their peculiar shape, or disagreeable parts, are inimicable to our Nature; but however, capable of subsisting in our Juices and vessels, and which being drove to the Lungs by the circulation of the blood, … or which possibly being carried about by the air, may be immediately conveyed to the lungs by that we draw in…'

Among the authors of books and pamphlets about the 1722 Marseilles outbreak of plague was a French doctor called Jean-Baptiste Goiffon (1722). After graduating, he worked with the French and Italian armies, during which time he became convinced that many diseases were caused by animalcules. Moreover, he gave a clear description of how an epidemic could develop and spread (translation; Williamson 1955):

> 'I think it cannot be denied, without doing violence to one's reason, that it is impossible to explain the effects of the plague and especially its mode of spread and its recurrence, by assuming the cause to be inanimate. One must of necessity suppose some small invisible insect, which by successive multiplication and reproduction continues to produce an agent as powerful as that from which it arose. Such a property belongs only to animate things, if an inanimate substance, as a grain of salt, e.g. were subdivided 1000 times, no one would believe that each could be as powerful as the original grain. Ordinarily the initial cause of the plague is small and confined, in order to spread throughout a town, a province or a realm, …. It must multiply. That is, Instead of the effects of the particles diminishing, as they would if inanimate, the number of infected people increases.'

The Italian physicians Carlo-Francesco Cogrossi (1682–1769) and Antonio Vallisneri (1661–1730) also made the link at a time when epidemics were sweeping across Europe. The plague, cholera, smallpox, and typhoid fever were claiming many victims, and infectious animal diseases regularly decimated flocks and herds. Rinderpest, a highly infectious cattle plague, threatened to spread from Padua and devastate the herds in Venice and its surroundings in 1713 (Santer 2015, DeLacey 2016). The leading physicians of the day were called in, and quarantine measures sometimes halted the spread of the epidemics. These measures were based on the hypothesis that disease must be spread by something, even though the nature of that contagion was not known.

One of the most enthusiastic of the Contagionists was Richard Bradley. He was a botanist, horticulturalist, and the author of a wide range of books on gardening methods and other subjects including housekeeping and cookery (Hamshaw Thomas 1952, Egerton 2006). He frequently included letters from his contacts to support his points. In 1712, he became a Fellow of the Royal Society of London and in 1724 was appointed as the first Professor of Botany at the University of Cambridge. At that time, Bradley was unusual because he developed his theories from practical observations and experiments. He regularly mentioned his use of microscopes, one of which was almost certainly a single-lens microscope known today as a Wilson–Hartsoeker (described in Clay

and Court 1932). His samples included the fungi consuming a cut melon (Fig. 3; Bradley 1714) and the 'insect eggs' similar in size to Van Leeuwenhoek's animalcules consuming his cauliflowers (Bradley 1718). He gave a 2-page description of how to carry out Van Leeuwenhoek's pepper water experiment (Van Leeuwenhoek 1676, Bradley 1739). It did not matter what he called them, Bradley clearly appreciated the place of microorganisms in the natural world, and he spent much time investigating them. When quoting Van Leeuwenhoek, he frequently also used the work of Hooke (1679) to support it.

A clergyman, John Lawrence, reported that grafting a yellow and green variegated bud onto a plain green jasmine tree caused the tree to gradually become variegated and the colour spread from the graft point so that eventually the whole tree was changed (Lawrence 1714). Bradley realised that this was an infection, describing the variegation as a 'distemper' (Bradley 1726). He repeated the experiment on other plants, using the results to illustrate his idea that sap circulates within plants just as blood does in animals, mentioning that it was the Turkish method of inoculation against smallpox that gave him the idea (see below). Gradually, he used such observed similarities to build his Germ Theory.

'By the foregoing Accounts we may observe, that Mankind, Quadrupeds and Plants seem to be infected in the same manner, by unwholesome insects; only allowing this difference, that the same Insect which is poisonous to Man, is not so to other Animals and Plants. All Pestilential distempers, whether in Animals or Plants, are occasion'd by poisonous insects convey'd from Place to Place by the Air'. (He used '*insects*' as a synonym for '*animalcules*'; Bradley 1721).

In his book 'New Improvements of Planting and Gardening, both philosophical and practical' (Bradley 1739), he expanded on his idea, pointing out that there are insects that attack different plants, using the arrival of diseases of fruit trees at different times of the year as an example. Similarly, animals and humans are affected by different infections. He suggested that some 'insects' may also have others that attack them.

Bradley was not rich, and there was no financial support associated with his Professorship. His books were needed to generate an income. Many of his botanical experiments were done in the gardens of Robert Balle's Camden House in Kensington, and he lost many of his plants when Balle went bankrupt and fled to Italy in 1721 (Fisher 2001). His appointment as Professor incurred the anger of John Martyn and his son, the 2nd and 3rd Professors of Botany at Cambridge who used their positions as editors of the Grubb Street Journal (Williamson 1961) to destroy Bradley's reputation, even after his early death. The value of his work in linking animalcules and contagion was thus only really recognised in the middle of the 20th century by Hamshaw Thomas (1952).

Finally, from the viewpoint of the 21st century, one cannot help wondering whether consideration of the working of vaccination and quarantine might have provided more evidence for the activity of animalcules.

It often surprises people to learn that forms of vaccination were known long before it was 'officially' discovered by Edward Jenner in 1792 (Cameron 1949). Scientists in Europe and America had become aware of inoculation against smallpox in Asian, Chinese, and African countries at least 100 years earlier. For example, there were frequent letters on the subject published in the 18th century Philosophical Transactions of the Royal Society of London. A total of three methods were reported. The Chinese dried scabs from smallpox pustules, ground them, and blew the resulting powder into the noses of their patients (Sloane 1755). The Turks of Constantinople had apparently been taking pus from the pustules of people who had had a mild dose of smallpox or from tubercles, and inserting it into cuts in the skin of the person to be inoculated (Timonius 1713). A third method used silk thread that had been soaked in pus, dried, and stored, possibly through several generations, until needed when it was threaded under the skin (Kochhar 2011).

After Lady Mary Worsley, wife of the British Ambassador to Constantinople, reported on her return to England about 1721, inoculation procedures were tested in London using prisoners (Sloane 1755, Stearns and Pasti 1950), who were then sent to work in a hospital treating smallpox patients. One woman prisoner shared a bed with a smallpox patient for about 6 weeks, remaining healthy. A second round of testing used 'charity children' from a local hospital. The procedure became fashionable after Lady Mary persuaded Caroline, Princess of Wales, to have her own children inoculated in 1722 (Weiss and Esparza 2014).

Quarantine, in many forms, has been practiced in many countries from classical times and deserves a review in its own right, but only couple of brief examples will be mentioned. The most obvious and widespread was the isolation of people with leprosy. Whatever a culture believed the cause of this terribly disfiguring disease to be, the response was similar—isolation, often to the extent of establishing specific hospitals attached to religious establishments. When plague was raging in France in the 17th century, quarantine was strictly applied to shipping and seamen, to the extent that the Dutch ordered that ships from Venice, their contents and the clothing and effects of crew and passengers were all burned (Bradley 1721). On the other hand, sometimes churchmen protested when infected people were sealed into their houses (Table 1).

Why did acceptance die away?

The Contagionist theory might have been more rapidly accepted if Antoni van Leeuwenhoek had supported it. He must have been aware of the reports in the Proceedings of the Royal Society, which he often mentioned as having received. In addition, Bradley and others had visited him. However, in 1722, Hans Sloane, via James Jurin, (former and current Secretaries of the Royal Society, respectively), asked him to look for his animalcules in 'itch blisters' (now called scabies; Rusnock 1996) because Dr G.C. Bonomo had reported that after watching peasant women opening Itch pustules on their children and squeezing whatever came out between their nails, he tried it himself and was able to extract what looked like a small white globule. Under his microscope, he found that this was a little insect (a scabies mite) and when drawing one using his microscope, he saw it produce an egg. He went on to reveal his irritation with those who would deny biological causes of medical problems (Bonomo and Mead 1703):

> 'From this discovery it may be no difficult matter to give a more rational account of the Itch than authors have hitherto delivered us. It being very probable that this contagious disease owes its origin neither to the melancholy humour of Galen, nor the corrosive acid of Sylvius nor particular further ferment of Van Helmont of the irritating salts in the serum or lympha of the moderns, but is no other than the continual biting of these animalcules…'

He went on to point out that all of the successful treatments for the Itch are powerful enough to kill the vermin lodged in the cavities of the skin. Sloane (Rusnock 1996) also asked about smallpox, an interest of his at the time.

Antoni van Leeuwenhoek replied in July 1722 (Rusnock 1996) with his reasons for not believing that animalcules cause small-

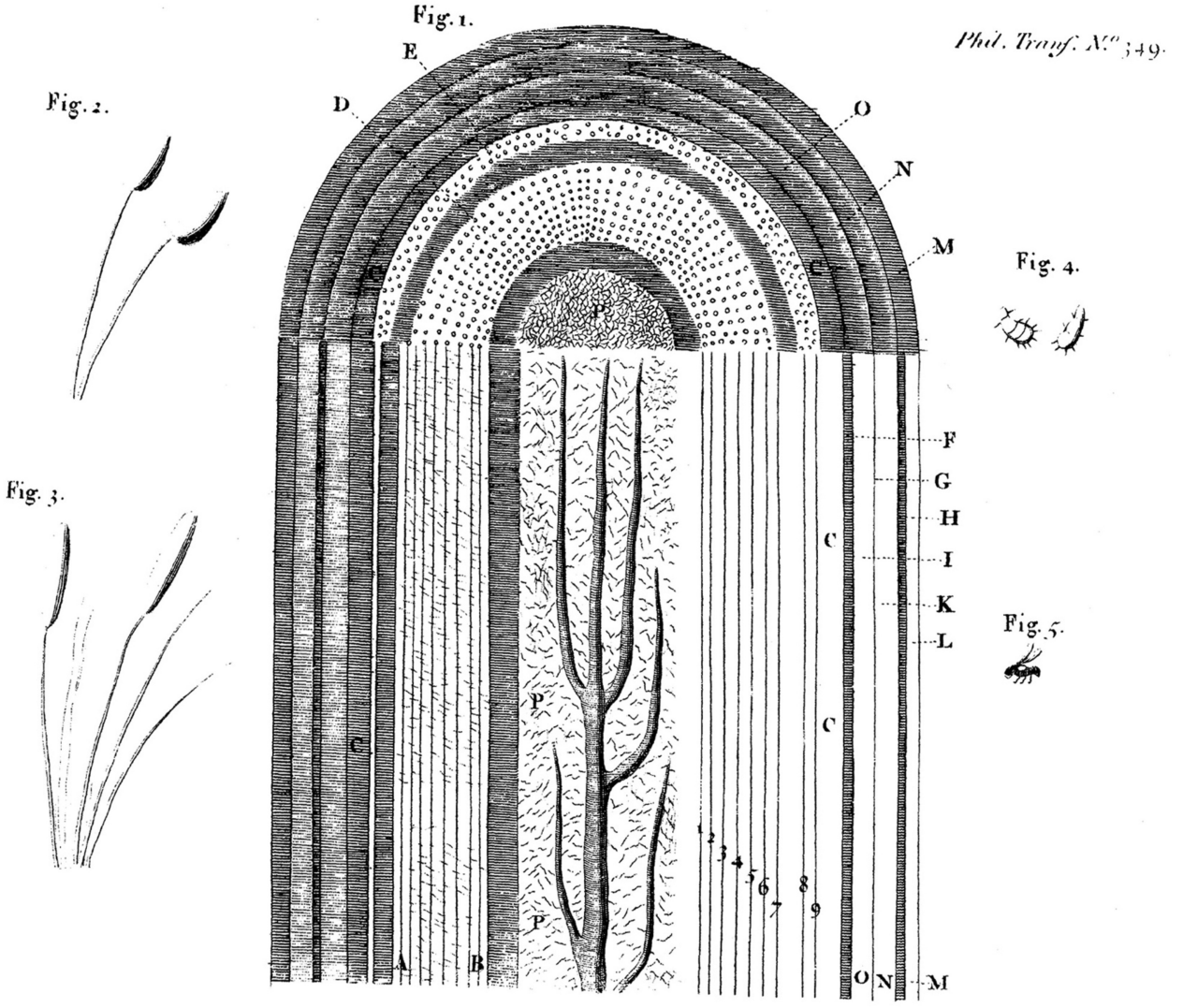


Figure 3. The figures that accompanied Bradley's paper on fungal grown on a melon (Bradley 1714). Figures 2 and 3 show fungal spore heads, which he examined under his Campani microscope and observed to be full of thousands of spores. Figures 4 and 5 show a maggot ('worm') and its fly. The large Fig. 1 shows a section of a rose stem, cut to support his theory about the movement of sap.

pox or other diseases. He seems to have considered all blisters (or pustules) on the skin as having the same cause. For example, he said that when he sat in the hot sun for too long, any exposed skin developed little blisters. Similarly, in the very cold winter, his hands and feet developed little blisters full of water. To the modern eye, those blisters were probably sunburn and chilblains, respectively. In his previous letter to Jurin in June 1722 (Rusnock 1996), he mentioned his belief that measles and smallpox were due to a thickening of the blood and blockage of the small blood vessels, which could be relieved by fever. However, he was willing to compare the contents of Itch blisters with those of measles and smallpox as soon as the local orphanage could provide children with the infections. Of course, measles and smallpox are both caused by viruses, which he could never have seen with his microscopes, unlike scabies larvae. Sadly, this was to be the last letter sent to the Royal Society during his lifetime, and word of his death in 1723 arrived in a letter to Jurin from Peter Gribius (Dobell 1932, Rusnock 1996), Minister of the New Church in Delft.

Despite Van Leeuwenhoek's views, there seems to have been a growing realisation that something that causes disease could be transferred among people. Why else would they have sent prisoners to nurse smallpox patients when they were evaluating the inoculation process? From the perspective of the 21st century, it seems odd that most people did not associate the working of inoculation with some form of 'animalcule' causing the infection. Of course, the causative viruses could never be seen in smallpox pus, even when using the best light microscopes.

The mechanical philosophers

Persuading people to accept new scientific discoveries has never been easy. In this case, the situation was particularly complex, especially when the Mechanical Philosophers and their admirers would not concede any importance to biological phenomena. This group included Edmund Halley, Isaac Newton, and Robert Boyle, all senior members of the Royal Society. For example, Boyle described a lady who had caught smallpox 'from her imagination', and claimed that all plague stopped when the sun entered the constellation of Cancer (Shaw 1725).

The publication of work that did not involve physics or mathematics was largely neglected, while Edmund Halley was responsible for the publication of the Royal Society's Proceedings (1713–1721) and James Jurin had to renew contact with Van Leeuwen-

hoek when he became Secretary of the Society (Rusnock 1996), apologising for the neglect of the previous years. This has actually benefitted Van Leeuwenhoek researchers since the Proceedings normally published edited highlights of his letters. When he decided to self-publish his work, he published the entire letters with their illustrations. These publications are in Dutch or Latin and are listed on the website 'Lens on Leeuwenhoek' (Anderson 2021).

Richard Mead FRS FRCP (1673–1754) is a good example of the influential people who supported the Mechanical Philosophers. He studied medicine in Leiden and Padua, then opened a successful medical practice in London when he became the personal doctor of Isaac Newton, Queen Anne, and King George II, among others. His books extensively quote classical scholars especially Galen, Hippocrates, and Pliny, and the conclusions drawn in his books were based on their work and the calculations of the Mechanical Philosophy group as well as his own ideas. For example, in a book about the influence of the sun and moon on diseases (Mead 1712) he claimed that health and disease were controlled by the pressure of the air, and that this was in turn controlled by the sun and the moon. His proposal was that since the sun and moon cause tides in water, they must also do so in air, preventing the accumulation of '*deadness and stinking air*'. When discussing 'pestilential contagion', and how it spread (Mead 1720), he suggested three possibilities, the first two of which were based on his theories of 'bad air':

(1) 'But to return to the Consideration of the Air, which we left in a putrid State: It is to be observed, that Putrefaction is a kind of Fermentation, and that all Bodies in a Ferment emit a volatile active Spirit, of Power to agitate, and put into intestine Motions, i.e. to change the Nature of other Fluids into which it insinuates it self.'
(2) 'The Blood in all Malignant Fevers, especially Pestilential ones, at the latter End of the Disease, does like Fermenting Liquors throw off a great Quantity of active Particles upon the several Glands of the Body, particularly upon those of the Mouth and Skin, from which the Secretions are naturally the most constant and large. These, in Pestilential Cases, although the Air be in a right State, will generally infect those, who are very near to the sick Person; otherwise are soon dispersed and lost: But when in an evil Disposition of This they meet with the subtle Parts, its Corruption has generated, by uniting with them they become much more active and powerful'.
(3) 'The third Way, by which we mentioned Contagion to be spread, is by Goods transported from infected Places. It has been thought so difficult to explain the Manner of this that some Authors have imagined Infection to be performed by the Means of Insects, the Eggs of which may be conveyed from Place to Place, and make the Disease when they come to be hatched. As this is a supposition grounded upon no manner of Observation, so I think there is no need to have Recourse to it'.

Bearing in mind that at this time, microorganisms were frequently called 'insects', it is ironic that the option that he considers does not require discussion (3) was the only one which approached the truth. The medical establishment was strongly against the linking of animalcules and infection, and many publications, even those in the Proceedings of the Royal Society (see above), were ignored.

There were also many who tried to support both sides of the argument at the same time. For example, in his book on the plague, Joseph Browne (1720), a popular quack doctor, began with a very flattering reply to Dr Mead's book, but by page 16 he seemed to be trying to occupy both sides of the fence:

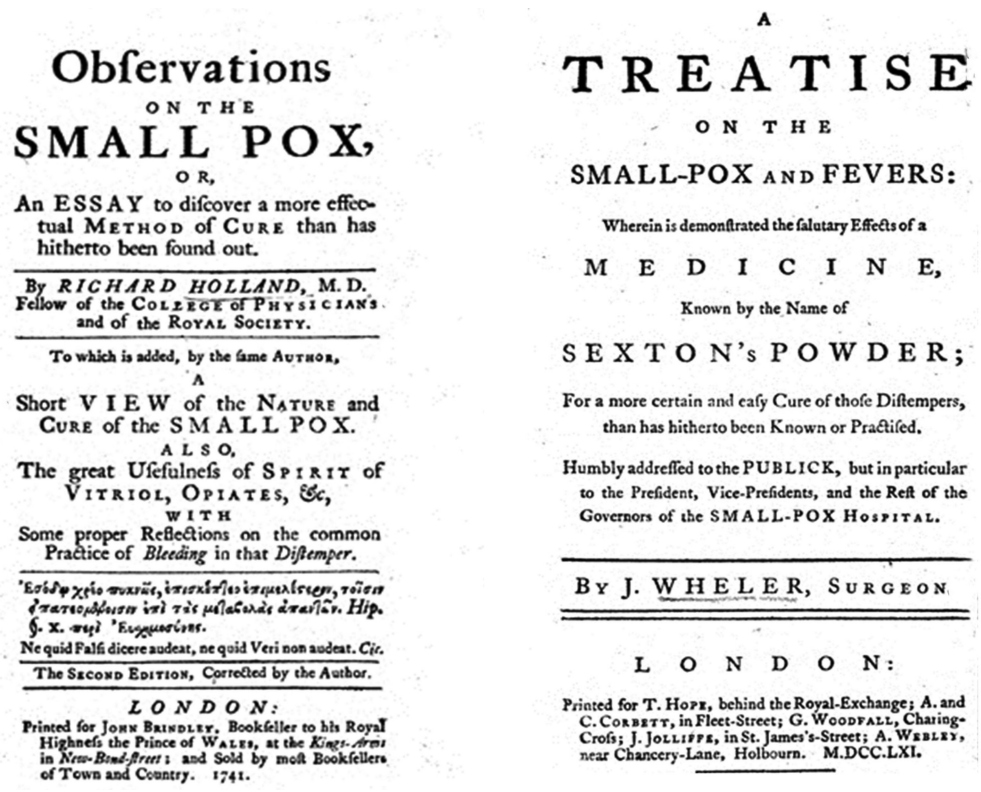
> 'But I humbly beg leave to be indulged a little further, in relation to this Point of Infection being conveyed by the Means of Insects. The Power and Efficacy of Worms and Insects, to procure Diseases … is very extensive and the Vulgar have not only err'd in this, if it be an Error, but many learned Physicians and Naturalists have been, and are still of Opinion, that the Plague arises from an animated or living Putrefaction. Kircher, in his Treatise of the Plague, brings this upon the Stage; from whence the Learned at that time asserted, that the Air might be demonstrated to be Verminous by the Microscope; which seems to stand confirmed by Malhighius (sic), Leuwenhoeck, Morgagni, Redi and Mangetus.'

Such books and pamphlets became very popular as printing became common and less expensive, and writers discovered that the public would buy claimed 'cures'. The result was very similar to 21st century outbreaks of 'fake news'. For example, in 1741, Richard Holland claimed to be curing smallpox with spirit of vitriol and opiates, and J. Wheler wrote in 1761 that smallpox could be cured with Sexton's Powder (Fig. 4). 'Cures' were published frequently and by 1785, a former gingerbread baker, Nathaniel Godbold, had made a fortune from his patented cure for consumption (aka tuberculosis) called Vegetable Balsalm (Featured Image). By keeping the complicated recipe within his family and extending his range of claimed cures, he was able to buy a country mansion (Godbold 1785, Macintosh 2016). Joel Shew claimed to cure cholera with cold baths in 1849 (Featured Image).

Conclusion

As mentioned in the introduction, this paper shows that acceptance of the idea that animalcules were linked to infectious disease steadily increasing for a time, but then faded away. There was no single reason why this should happen. Antagonism from the Establishment, as described here, did not help, but was probably not the most important factor.

Science based on fact was in its infancy. The biggest problem was possibly the lack of even simple microbial systematics that could have separated the vast and diverse group of animalcules into protozoa, algae, bacteria, and other microorganisms, and allowed evaluation of observations. Van Leeuwenhoek's simplistic belief that all blisters would have the same cause is an example. If he did not find little animals in his sunburn and chilblain blisters, he assumed that there would none in others. He was even doubtful of the report that scabies mite larvae were causing them, despite Bonomo's work. He was also not convinced that animalcules were involved in inoculation. Something else in the pus must be making inoculation work. Nobody would see the cause of smallpox blisters until the advent of the electron microscope centuries later. Van Leeuwenhoek might even have been remembering the time in 1677 when Johan Ham brought him samples from a patient which contained 'animalcules', asking whether they were causing the patient's venereal disease (Van Leeuwenhoek 1678). Van Leeuwenhoek could prove that all males, ranging from insects to humans and healthy or not, produce such animalcules (Lammers 1974, Robertson et al. 2016). The spermatozoa could, therefore, not be the cause of the disease. Bradley's germ theory and his observation that similar-looking diseases in different animals or plants were specific to their host animal or plant was an indication that the diseases were not simply chemical effects, but



Observations
ON THE
SMALL POX,
OR,
An ESSAY to discover a more effectual METHOD of CURE than has hitherto been found out.
By RICHARD HOLLAND, M. D.
Fellow of the COLLEGE of PHYSICIANS and of the ROYAL SOCIETY.
To which is added, by the same AUTHOR,
A
Short VIEW of the NATURE and CURE of the SMALL POX.
ALSO,
The great Usefulness of SPIRIT of VITRIOL, OPIATES, &c,
WITH
Some proper Reflections on the common Practice of *Bleeding* in that *Distemper*.
Ne quid Falsi dicere audeat, ne quid Veri non audeat. *Cic.*
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Printed for JOHN BRINDLEY, Bookseller to his Royal Highness the Prince of WALES, at the *Kings-Arms* in *New-Bond-Street*: and Sold by most Bookfellers of Town and Country. 1741.

A
TREATISE
ON THE
SMALL-POX AND FEVERS:
Wherein is demonstrated the salutary Effects of a
MEDICINE,
Known by the Name of
SEXTON's POWDER;
For a more certain and easy Cure of those Distempers, than has hitherto been Known or Practised.
Humbly addressed to the PUBLICK, but in particular to the President, Vice-Presidents, and the Rest of the Governors of the SMALL-POX HOSPITAL.
BY J. WHELER, SURGEON
LONDON:
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Figure 4. The title pages of Holland's and Wheler's pamphlets claiming cures for smallpox (Holland 1741, Wheler 1761). These are examples of the many books and pamphlets about fake cures on sale in the decades between the death of Van Leeuwenhoek and the publication of the discoveries of Koch, Pasteur, and Beijerinck. Featured Image: fake cures—Godbold's cure for tuberculosis and Shew's cure for cholera.

the value of his work was not recognised until the middle 20th century (Hamshaw Thomas 1952).

Of course, methods and equipment tend to only be developed after the need is recognised. Experiments had to be repeatable. Understanding that animalcules could be identified by biological and biochemical characteristics had to wait for someone to recognise the value of axenic cultures and the existence of cell biochemistry. Accurate bacterial morphology required achromatic lenses and phase contrast lighting and viruses, of course, had to wait for the electron microscope. True conviction had to wait for the end of the 19th century and the discoveries of Robert Koch, Louis Pasteur, and Martinus Beijerinck.

Even now, with all the 21st century knowledge and equipment at our disposal, it has proved impossible to convince a lot of people that viruses exist and can make one ill. Fake news has migrated from the penny pamphlets of the 18th century to the internet, and the objections of the Church and medical establishment are now provided by 'defenders of liberty' and others.

Why would people in the 17th, 18th, or even 19th centuries believe in creatures so small that they could not be seen, when others with impressive titles and fortunes claimed that opiates, bleeding, or a herbal mixture was all that was needed (Fig. 4).

Sources of antique books

- Most of the 17th and 18th century books can be found as PDF downloads from the Internet Archive archive.org. A few are available on Google Books.
- The first 15 volumes of Van Leeuwenhoek's work can be downloaded as PDFs from DBNL *Digitale Bibliotheek voor de Nederlandse Letteren*. Den Haag: Royal Library. https://www.dbnl.org/zoeken/zoekeninteksten/.
- Related publications in the Proceedings of the Philosophical Transactions of the Royal Society can be found in their online archive: http://rstl.royalsocietypublishing.org/content/by/year

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