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THE DEVELOPMENT OF THE VIRUS CONCEPT AS REFLECTED IN CORPORA OF STUDIES ON INDIVIDUAL PATHOGENS*

5. SMALLPOX AND THE EVOLUTION OF IDEAS ON ACUTE (VIRAL) INFECTIONS

by

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IN 1806, Thomas Jefferson was in his second term of office as the third President of the United States. From his neo-classical mansion of Monticello in Virginia, Jefferson wrote on 14 May a letter to Edward Jenner, congratulating him on his discovery of vaccination which Jefferson helped to promote in the United States. After comparing Jenner's discovery favourably with William Harvey's discovery of the circulation of the blood, Jefferson continued in somewhat purple prose: "You have erased from the calendar of human afflictions one of its greatest. Yours is the comfortable reflection that mankind can never forget that you have lived; future nations will know by history only that the loathsome small-pox has existed, and by you has been extirpated . . .".[1] The optimism voiced by Jefferson proved to be highly premature. In the last decade, the vast resources of the World Health Organization have been brought to bear on the problem of world-wide eradication of variola; even so, the last pockets of infection have proved more persistent than expected, and optimistic estimates far more recent than Jefferson's remain so far unfulfilled.[2] On the other hand, in the absence of an animal carrier of the virus of smallpox, complete eradication may be obtained with the help of vaccination, while bubonic plague, carried by a number of rodents, remains endemic over large areas of the globe, including North America. Thus twentieth-century public health authorities still face some degree of challenge from the two major scourges of mankind, which through massive epidemic outbreaks exercised natural population control throughout medieval and early modern history.

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[1] The letter is quoted in its entirety by Baron: John Baron, *The life of Edward Jenner, M.D.*, London, Henry Colburn, 1838, vol. 2, pp. 94–95.

[2] The imminent complete eradication of smallpox was predicted in 1976, after ten years of the "intensified global eradication programme" launched by the World Health Organization in January 1976. D. A. Henderson wrote: "The world may have seen its last case of the most devastating disease in human history. Smallpox . . . is making its last stand in two remote areas of Ethiopia, one in the desert and one in the mountains . . . ." (D. A. Henderson, 'The eradication of smallpox', *Scient. Am.*, 1976, **235** (4): 25–33, p. 25). Since then, war in Ethiopia has added to the problems faced by the WHO teams, and the target of complete global eradication remains in question; on 19 April 1978, the WHO announced the offer of a global reward for any report of a case of smallpox.

In trying to assess the influence wielded by smallpox on social and political history, or just to determine the chronology of the disease, one is hampered by the inability to identify the disease with any degree of certainty from extant descriptions before A.D. 900, and sometimes much later. The virus of smallpox is known to vary in virulence,[3] and inaccurate or inadequate descriptions of the clinical picture offer rich opportunities for confusion with a number of other fevers accompanied by rashes and pustules. Dixon[4] has provided a sober account of the known early history of the disease, and of the difficulties inherent in attempts to identify it in retrospect. He points out that the abundant lesions on the face and body of the mummified Rameses V, who died about 1100 B.C. of an acute infectious disease, are very similar to those of malignant smallpox. It is therefore curious that there is no mention of smallpox in Hippocrates' otherwise copious volumes of clinical descriptions, nor elsewhere in the Greek and Roman medical literature according to Dixon, although some other authors have attempted to identify destructive epidemics which contributed to the decline of the Roman empire in the third and fourth centuries as outbreaks of smallpox.[5]

Nor does contemporary terminology in any way clarify the issue. Even when the term "variola" first appeared[6] it was not accompanied by a clinical description, and we have no way of knowing whether or not it referred to smallpox. For several hundred years after the introduction of the terms "variola" and "morbilli", the diseases they refer to can in no certain way be distinguished as smallpox and measles, respectively, on the basis of the inadequate clinical descriptions. In the case of smallpox, the confusion with chicken-pox further clouds retrospective epidemiological considerations.[7]

The first identifiable account of smallpox is found in the Arabic medical literature of the tenth century.[8] Its author was Abū Bakr Muḥammad Ibn Zakariyya al-Rāzī,

[3] Within the three major types of smallpox, case fatality ratios vary considerably in individual outbreaks. The following values were given recently by J. H. Nakano: *Variola major* (case fatality ratio 15-40 per cent); *variola intermediate* (case fatality ratio 5–15 per cent); and *variola minor*, or alastrim (case fatality ratio below one per cent). J. H. Nakano, 'Comparative diagnosis of pox virus diseases', in E. and C. Kurstak (editors), *Comparative diagnosis of viral diseases,* New York, San Francisco and London, Academic Press, 1977, vol. I, part A, p. 290.

[4] C. W. Dixon, *Smallpox*, London, Churchill, 1962, see chapter 10.

[5] A vivid tale of the pestilence which decimated the Roman armies in Mesopotamia in A.D.165, and a discussion of Galen's description of it, and of its claim to have been smallpox, may be found in Julius Petersen, *Kopper og Koppeindpodning*, Copenhagen, Gyldendal, 1896, pp. 7–10. Petersen himself was doubtful of its identity. Arturo Castiglioni, in *A history of medicine,* New York, Alfred A. Knopf, 1947, p. 244, suggests that it may have been an epidemic "of exanthematous typhus, but perhaps of bubonic plague". He does, however, believe that "Cyprian's pestilence", which lasted from A.D. 251–266 may have been smallpox, whereas Petersen believes this to have been plague (pp. 10–11).

[6] The term "variola" was introduced by Marius, Bishop of Avenches, at the time of "Justinian's pestilence", which may or may not have been smallpox, about A.D. 570.

[7] See Wilhelm Ebstein, 'Zur Geschichte der Windpocken und deren Verhältnis zu den Pocken', *Janus*, 1906, **11**: 181–195; 240–252.

[8] Centuries later, Voltaire was to refer to smallpox as "this accursed Arabic pest" (letter to the Chevalier de Lisle, dated 27 May 1774; quoted by M. S. Libby in *The attitude of Voltaire to magic and the sciences,* New York, Columbia University Press, 1935, p. 251)—not a wholly justified attribution. Voltaire's outburst was provoked by the illness and death, on 10 May 1774, of Louis XV from smallpox.

better known in the West as Rhazes, who distinguished clinically between smallpox and measles.[9] He believed that smallpox attacked primarily young children, and that in the exceptional cases seen of the disease occurring in young men, the individuals affected were susceptible because of an earlier attack of chicken-pox. The curious reasoning behind this belief was based on Rhazes' conviction that the aetiology of these diseases was closely connected with the changing conditions of the blood. He had a theory that the "unfermented" blood of infants passed through a stage of fermentation in growing children, until it reached its optimum condition in young adult men in whom it ". . . may be compared to must which has already fermented and made a hissing noise, and has thrown out abundant vapours and its superfluous parts, like wine which is now still and quiet and arrived at its full strength . . .".[10]

The uncertainty with regard to the history of the disease is reflected already in the writings of Rhazes. He was personally convinced that Galen had known and mentioned smallpox; but he was forced to admit that there was little detail in Galen's writings, at least in the part he had read which had been "published in Arabic". As for the remaining parts of Galen's corpus of work, Rhazes informs his readers that he has consulted "those who use both the Syriac and Greek languages", but that they could add nothing to his information, and ". . . indeed most of them did not know what [Galen] meant by those passages which I have distinctly quoted".[11]

The Arabic school, so ably represented above all by Rhazes and, nearly a century later, by Avicenna, held sway throughout the Dark Ages and the early Middle Ages. Their followers believed without reservations in the "sweating regimen", the treatment first recommended by Rhazes (although he did also recommend initial cooling, cupping, and blood-letting in order, if possible, to prevent eruption), and subsequently adhered to, to the discomfort, if not worse, of the patients. The treatment consisted in covering up the patient (already well equipped with "a double shirt, with the upper border closely buttoned") in heavy blankets in an over-heated room, and administering "heating medicines and cordials". To complete the stifling qualities of the sick-room Rhazes recommended placing underneath the patient's bed ". . . two small basins of boiling water, one before and the other behind him, so that the vapour may come to the whole body except the face; and the skin may be rarefied, and disposed to receive and evaporate the superfluous humours . . .".[12]

Six centuries later, Thomas Sydenham revolutionized the treatment of smallpox by boldly recommending the complete antithesis of the teaching of Rhazes and of later writers. Sydenham countered the heat therapy still in vogue in the seventeenth century with his "cooling regimen", which he believed helped nature to do ". . . her own work at her own rate; both excreting and expelling the morbific matter in due course and time".[13] Sydenham's clear-cut and still valid directions for the treatment

[9] Rhazes' 'Treatise on the smallpox and measles' was translated from the Arabic original into English by W. A. Greenhill and published in London for the Sydenham Society in 1847. The text is reproduced in *Med. Classics*, 1939, **4** (i): 22–84.

[10] Ibid., p. 26.

[11] Ibid., p. 25.

[12] Ibid., pp. 37–38.

[13] *The works of Thomas Sydenham, M.D.*, translated from the Latin edition of Dr. Greenhill with a life of the author by R. G. Latham, London, Sydenham Society, 1848, vol. I, see p. 135.

of smallpox patients were not matched by clarity of thought on the subject of the aetiology of the disease. They could hardly have been in the context of his time. The vagueness of his reasoning is reflected in the different interpretations of his writing on the subject by different authors. Thus Dewhurst commented that ". . . he still regarded the disease as being due to a new texture of the blood, rather than the result of widespread infection; in his view smallpox was physiological renewal, rather than pathological invasion, of the blood".[14] This might leave the reader with the impression that although Sydenham had improved upon the clinical treatment recommended by Rhazes, he had added little to his basic concepts. Keele, on the other hand, was struck by the preoccupation of Sydenham, supposedly "the clinical observer untrammelled by theory", with ". . . a mass of speculative theoretical statements about 'morbific particles', 'peccant matter', etc., in disease". Keele went on to show that Sydenham's concept of "morbific particles" was strongly influenced by the theories of his friend, Robert Boyle.[15] Dixon reiterates that Sydenham did not consider smallpox to be infectious.[16]

Our views of Sydenham's attitude to theories of infection and contagion could well depend on which parts of his works we happen to read. On the subject of smallpox, he acknowledges its contagious nature with the remark: "It attacks whole families with its contagion, sparing no one . . .",[17] but later disarmingly admits: "As to what may be the *essence* of smallpox, I am, for my own part, free to confess that I am wholly ignorant; this intellectual deficiency being the misfortune of human nature, and common to myself and the world at large". Having made this reservation, he continues: "Nevertheless, when I carefully weigh the evidence derived from the above-named symptoms, it suggests to me the idea of inflammation; of an inflammation both of the blood and the humours. In clearing herself of this, Nature is at work during the first two or three days, striving at the digestion and concoction of the inflamed particles, with the intention of afterwards discharging them upon the surface of the body, for the sake of maturation, and finally expelling them from her boundaries under the form of little abscesses".[18] It does seem fair to conclude that within the limits imposed by contemporary knowledge and thinking, Sydenham certainly did not rule out processes of infection, and that he may even have spared a thought for something not unlike reactions which a much later age was to call immune response.

Nevertheless, there is little improvement in the above on the theories of Fracastoro, who in 1546 wrote, on "the poxes and measles" that "Both kinds of pustules presently fill up with a thin sort of pituita and matter, and the malady is relieved by these very means . . . [these fevers] are contagious, because what exhales from the putrefaction is very viscous, and is a germ of contagion for another individual in the same manner as I have described in other diseases".[19] On the other hand, Fracastoro still

[14] Kenneth Dewhurst, 'Sydenham's original treatise on smallpox with a preface, and dedication to the Earl of Shaftesbury, by John Locke', *Med. Hist.*, 1959, **3**: 278–302, see p. 300.

[15] Kenneth D. Keele, 'The Sydenham-Boyle theory of morbific particles', ibid., 1974, **18**: 240–248.

[16] Dixon, op. cit., note 4 above, see p. 195.

[17] Sydenham, op. cit., note 13 above, see p. 123.

[18] Ibid., p. 133.

[19] Hieronymi Fracastorii, *De contagione et contagionis morbis et eorum curatione*, translation and notes by Wilmer Cave Wright, New York and London, G. P. Putnam's Sons, 1930, see p. 75.

adhered strictly to Arabic tradition in recommending an unalleviated heating regimen, including pore-opening decoctions. Fracastoro's sixteenth-century mind did not exclude elements of mysticism from his thinking; the effects of unfortunate constellations of the planets and related phenomena were also taken into consideration.[20] A century later, Sydenham believed that the pattern of epidemics was determined by what he called "epidemic constitution", and this in turn depended upon certain mysterious atmospheric conditions. Aided by contemporary meteorological studies by his friends Robert Hooke and John Locke, he attempted to demonstrate a correlation between annual weather patterns and the occurrence of epidemics.[21] When the attempt not surprisingly failed, he concluded that the different "constitutions" found in different years with similar prevailing weather patterns must be due to "hidden and inexplicable changes within the bowels of the earth".[22] Such reasoning was easily accepted at a time when an endemic situation was explained as the omnipresence of the "seed" of smallpox, to be activated by adverse external circumstances or injudicious dietary measures. When inoculation was introduced in the eighteenth century, severe restrictions in diet and temperature were imposed prior to treatment in a misconceived effort to stave off ill effects. Not surprisingly, the results were sometimes disastrous; by mid-century when the practice of variolation had become a well-established fact, the more enlightened inoculators such as Sir George Baker[23] and Angelo Gatti[24] were well aware of the danger inherent in this approach and warned against it.

In discussing the views of Fracastoro and of Sydenham it is necessary to make certain reservations. Not only must they be seen in the context of their time, and not be judged by the exacting standards of later knowledge and terminology; but the problems are compounded by actual linguistic difficulties. Fracastoro's medieval Latin was not always easy to interpret;[25] Sydenham's English texts were translated by others into Latin, and subsequently retranslated into English by yet other authors.[26] With the eighteenth-century Enlightenment it became increasingly common to write in the vernacular, although problems presented by translations have continued.[27]

[20] Ibid.; for discussion of Fracastoro's attitude to astrology see introduction, p. xxxiii.

[21] From antiquity onwards, the influence of changes in the quality of the surrounding air on the pattern of epidemics had been widely accepted, and Sydenham's attitudes to "epidemic constitution", with attendant studies of the correlation between prevalence of disease and meteorological conditions continued into the nineteenth century; see Keele, op. cit., note 15 above.

[22] Sydenham, op. cit., note 13 above, see p. 33.

[23] Sir George Baker (1722–1809), whose main claim to fame is his perceptive account of the "Devonshire colic", wrote on smallpox in *An inquiry into the merits of a method of inoculating the smallpox,* London, J. Dodsley, 1766; and 'Observations on the modern method of inoculating the small-pox', *Med. Trans.*, 1772, **2**: 275–324.

[24] Angelo Gatti, *Réflèxions sur les préjugés qui s' opposent aux progrès et à la perfection de l' inoculation*, Brussels, Musier fils, 1764; and *Nouvelles réflèxions sur la pratique de l'inoculation,* Brussels, Musier fils, 1767.

[25] W. C. Wright (op. cit., note 19 above) says in his preface: "I have had before me the Lyons edition of *De Contagione,* 1554, but hardly any of the text of Fracastoro can be safely used without revision, and the Latin text here printed and translated is the result of a comparison by me of the Editio Princeps, 1546, the two Lyons editions, 1550, 1554, and the Editio Princeps of the *Opera Omnia*, 1555. . . ."

[26] See Dewhurst, op. cit., note 14 above, p. 301.

[27] In the history of smallpox inoculation, one example which comes to mind is Maty's English

Sydenham's writings on smallpox had been prompted by extensive and increasingly severe epidemics in England and on the European continent during the 1660s and 1670s. At this time we also find the first accounts of what has been seen as the seeds of the practice of variolation in Europe, but which in its origins was more closely related to witchcraft.[28] Thomas Bartholin of Copenhagen, famed as an anatomist rather than a pathologist,[29] called it "Transplantation of disease", and pronounced it "a stupendous remedy, by means of which the ailments of this or that person are transferred to a brute animal, or to another person, or to some inanimate thing",[30] a practice possible, according to Bartholin, in cases of smallpox, plague, syphilis, and dysentery. A more legitimate claim to have been a precursor of variolation can be made on behalf of the practice of "buying the smallpox", i.e. children being sent to buy crusts from mild cases of smallpox for a few pennies, which apparently was quite common in rural districts in a number of European countries towards the end of the seventeenth century.[31]

Whatever its origins, the superstitious practice of transference had become the, still to some extent superstitious, practice of inoculation or engrafting when Giacomo Pylarino[32] found it performed by a Greek woman during a serious outbreak of smallpox in Constantinople in 1701. When Pylarino subsequently informed the world of his discovery he still used the word "transference", while the term "inoculation" was introduced in an account of the practice rendered to the Royal Society in London by Emanuel Timone[33] in December 1713.[34] A year after the appearance of

translation (Angelo Gatti, *New observations on inoculation,* translated from the French by M. Maty, London, P. Vaillant, 1768) of Gatti's *Réfléxions* and *Nouvelles réfléxions*, especially a certain footnote (p. 32) which in Maty's translation—or rewriting—acquires a flavour distinctly different from that of the French original, and which in Maty's version has been used by recent authors as valid argument. One is reminded that Johnson, offered Maty as an assistant, remarked: "The little black dog! I'd throw him into the Thames first" (*Dictionary of national biography*).

[28] What Charles Creighton, in *A history of epidemics in Britain,* Cambridge University Press, 1891–94, called ". . . the 17th century practice of sympathetic transference of disease from one to another or from man to brute, or to plants, stones, holes in the ground, etc. . . ." (vol. II, p. 474).

[29] Thomas Bartholin (1616–1680), at Medical School at Leyden during the decade following the publication of William Harvey's *Exertatio anatomica de motu cordis et sanguinis in animalibus,* and later at Montpellier and Padua, was Professor of Anatomy at the University of Copenhagen from 1648; see Axel Garboe, *Thomas Bartholin,* Copenhagen, Ejnar Munksgaard, 1949.

[30] Creighton, op. cit., note 28 above, p. 474; the thought that cowpox could have originated in this way is intriguing, if unprovable.

[31] Ibid., pp. 471–472.

[32] Giacomo Pylarino (1659–1718) was born on the island of Cephalonia in the Ionian Sea, and graduated in both law and medicine at the University of Padua. His work was brought to the notice of the Royal Society through the intervention of William Sherard, F.R.S. (whose name is perpetuated in Oxford's Sheradian Chair of Botany), who at the time was British Consul at Smyrna, where Pylarino for part of his varied and colourful career served as Venetian Consul.

[33] Emanuel Timone (?–1718); his name is spelt in a variety of ways by different authors; this is the spelling he used himself in a letter quoted by Edward Wortley Montagu in his letter to Addison of 26 August 1717 (State Papers 97/24, Public Record Office, London). He was born of Italian parents on the island of Chios in the Aegean. It is evident from Montagu's letter that Timone practised politics not always of the most bona fide kind, in addition to medicine; he eventually committed suicide when political intrigue became too powerful—it has even been suggested that he was "shamed into despair and suicide by the machinations of Sir Edward Wortley Montagu". See R. P. Stearns, 'Fellows of the Royal Society in North Africa and the Levant', *Notes Rec. R. Soc. Lond.*, 1954, **11**: 77–78. Timone had medical degrees from both Padua and Oxford.

[34] Emanuel Timonius, 'An account, or history, of the procuring the small pox by incision, or

this tract in the *Philosophical Transactions*, Pylarino published in Venice a small book on the same subject,[35] which was in its turn reprinted in the *Philosophical Transactions* in 1716.[36] Timone's correspondent at the Royal Society, who presented his letter to the Society, was John Woodward, M.D., whose reputation among his peers did not help the acceptance of Timone's ideas by the Fellows of the Society.[37] In fact, remarkably little attention was paid to the papers by Pylarino and Timone until in 1721 serious outbreaks of smallpox on both sides of the Atlantic prompted Cotton Mather and Zabdiel Boylston in Boston to issue an edited version of both accounts.[38] At the same time, Lady Mary Wortley Montagu began her campaign in England for the introduction of the practice of "engrafting"[39] which had so impressed her in Constantinople.

Lady Mary possessed a strong personality and a restless intelligence which was ever searching for causes worth her attention and agitation. Her own early unhappy experience with smallpox[40] and the removal of her household to her husband's Constantinople Embassy in 1717 made her the champion of smallpox inoculation. When she was expecting her second child in Constantinople in 1717, Dr. Timone was physician to the family;[41] but there is no direct evidence in her letters of any influence by Dr. Timone on Lady Mary's decision to have her three-year-old son inoculated in Constantinople. The inoculation of her daughter in London at the time of the smallpox outbreak of 1721[42] provided Lady Mary with a natural focus from which to launch her most famous campaign.

The writings of Pylarino and of Timone on the one hand, and the more socially and politically directed agitation of Lady Mary and of the Princess of Wales[43] in London, and of Cotton Mather and Zabdiel Boylston in Boston, Massachusetts,[44]

inoculation, as it has for some time been practised at Constantinople', *Phil. Trans. R. Soc. Lond.*, 1714, **29**: 72–82.

[35] Jacobus Pylarinus, *Nova et tuta Variolas excitandi per Transplantationem methodus*, Venice, Gabriel Hertz, 1715. (See Figure 1.)

[36] Jacobus Pylarinus, 'Nova et tuta Variolas excitandi per Transplantationem Methodus, nuper inventa et in usum tracta', *Phil. Trans. R. Soc. Lond.*, 1716, **29**: 393–399.

[37] What the *Dictionary of national biography* called Woodward's "difficult temperament and unpleasing personality" had made him *persona non grata* with Sir Hans Sloane and the rest of the Establishment at the Royal Society, see R. P. Stearns, 'Remarks upon the introduction of inoculation for smallpox in England', *Bull. Hist. Med.*, 1950, **24**: 103–122.

[38] *A faithful abridgement of two accounts in the Philosophical Transactions: Some account of what is said of inoculating or transplanting the small-pox*, by the learned Dr. Emanuel Timonius, and Jacobus Pylarinus, Boston, S. Gerrish, 1721.

[39] Genevieve Miller, in her preface to *The adoption of inoculation for smallpox in England and France*, Philadelphia, University of Pennsylvania Press, 1957, has pointed out that the term "variolation" was not introduced until the era of vaccination—according to the *Oxford English dictionary* it first appeared in 1792.

[40] Contributing to what she herself regarded as disfigurement was the loss of her "very fine eyelashes"—see Miller, op. cit., note 39 above, p. 31.

[41] This is made clear from the letter referred to in note 33, as was first pointed out by Robert Halsband in 1953, see R. Halsband, 'New light on Lady Mary Wortley Montagu's contribution to inoculation', *J. Hist. Med.*, 1953, **8**: 390–405.

[42] It seems to have been a small outbreak of a particularly virulent strain, see Miller, op. cit., note 39 above, p. 71.

[43] Miller, ibid., pp. 70–90, has discussed these early campaigns in detail. She believes that popular versions have exaggerated the influence wielded by Lady Mary in introducing inoculation.

[44] The Mathers, Cotton and his father Increase, were characteristic representatives of the early

facilitated the acceptance of the practice of inoculation in certain educated circles in Europe and America during the eighteenth century. There was a great deal of unfavourable reaction as well, especially from factions of the medical profession and the Church. In France the opposition far outweighed the voices raised in defence of inoculation, in spite of support from Voltaire,[45] and acceptance of the practice was considerably slower than in England and America.[46] As a result of the controversy, much was written for and against inoculation throughout the century of the Enlightenment; and in medical terms, enlightenment was reflected in the more advanced views on infection and contagion being expressed in eighteenth-century writings on smallpox.

The Singers have reminded us that the 1720s were "peculiarly rich" in works attempting to understand the nature of infection.[47] A number of these were concerned especially with the plague;[48] Benjamin Marten wrote remarkably lucidly on consumption in a volume published in 1720,[49] in which he also included smallpox in a more general discussion of "Specific diseases due to specific organisms". Here Marten expounded his theory of specific "animalcula" inducing specific diseases "by means of their wonderful Smallness and injurious Parts".[50] Marten lived and wrote in London; according to Singer, he appears to have been a loner outside, or perhaps even deliberately ostracized by, the more influential circle of contemporary physicians who either ignored or obliquely attacked his publications.[51]

Ten years later Thomas Fuller published an account of eruptive fevers.[52] Fuller wrote at the end of a long life, after fifty years as a country practitioner at Sevenoaks, Kent; and in spite of the diffident, almost apologetic tone of his "Dedication", he made a number of points concerning the nature and specificity of smallpox and other eruptive fevers which certainly deserve a place in the conceptual history of infectious disease. There is no reason to doubt Fuller's claim to complete isolation in the country, and the works of Marten and of Fuller, for all the similarity of their basic concepts and the few years separating their publication, were independently conceived and written. Marten explained the different clinical pictures presented in

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puritan clergymen, and their narrow-minded intolerance was a moving force behind the Salem witch trials in 1662. But they were also scholars, and Cotton's interest in science was rewarded when he became the first native-born American (his grandfather, Richard Mather, had arrived in Boston, in the colony of Massachusetts Bay, with a party of Puritans on board the *James* in the spring of 1635) to be elected a Fellow of the Royal Society.

[45] In late 1723, Voltaire was seriously ill with smallpox. Shortly afterwards, he described his illness in a letter to Baron de Breteuil: ten years later, his experience was reflected in the eleventh of his *Lettres philosophiques*. For discussion of the letters and their background, see M. S. Libby, *The attitude of Voltaire to magic and the sciences*, New York, Columbia University Press, 1935, pp. 246–251.

[46] See Miller, op. cit., note 39 above, chapter 8, 'The adoption of inoculation in France'.

[47] Charles and Dorothea Singer, 'Development of the doctrine of contagium vivum 1500–1750', *Intern. Med. Congress*, 1913, *Sect. Med. Hist.*, pp. 187–205, see p. 205.

[48] Ibid.

[49] Charles Singer, 'Benjamin Marten, a neglected predecessor of Louis Pasteur', *Janus*, 1911, **16**: 81–89; the bulk of this paper is "word for word as Marten wrote it", see p. 82.

[50] Ibid., p. 84.

[51] Ibid., pp. 96–97.

[52] Thomas Fuller, *Exanthematologia; or, an attempt to give a rational account of eruptive fevers, especially of measles and smallpox*, London, C. Rivington & S. Austen, 1730.

plague, smallpox, measles, etc., by concluding that they were ". . . severally caused by innumerable Animalcula, or exceeding minute Animals that variously offend us according as their species are different".[53] Fuller resorted to metaphor to make his point very clearly: ". . . and therefore the Pestilence can never breed the Small-Pox, nor the Small-Pox the Measles, nor they the Crystals or Chicken-Pox, any more than a Hen can a Duck, a Wolf a Sheep, or a Thistle Figs; and consequently, one Sort cannot be a Preservative against any other Sort."[54]

Elsewhere in his absorbing text Fuller turned to the question of the path of transmission, and again in a few sentences dealt effectively with a problem which was to remain a bone of contention until it was finally solved by Koch and by Pasteur. He wrote: "The chief and commonest Way of taking contagious Fevers, Small-Pox, and Measles, is by Infection; that is, by receiving with the Breath, or thro' the Pores, such virose Corpuscles, as are peculiar for the Breeding of them";[55] and later: "My settled Opinion is, that in regard every Effect is necessarily such as its Cause, it must needs be, that every Sort of venomous Fevers is produced by its proper and peculiar Species of Virus."[56] In one respect did Fuller still carry forward the ideas of the Arabic school concerning the aetiology of the disease. Rhazes had considered smallpox an inevitable affliction, a necessary "fermentation" of an inherent, only vaguely characterized condition of the blood, and little had been added to this thesis in the writings of Fracastoro and Sydenham. By the late seventeenth and early eighteenth centuries such ideas had hardened into a belief in an innate seed of the disease, lying dormant until activated by external factors.[57] Fuller in 1730 attempted to combine elements of the traditional view with his ideas on contagion by postulating the presence in the blood of specific "Ovula" which required the introduction from outside the organism of an "afflatus genitalis" in order to produce the specific disease.[58]

During this period, the torch lit by Lady Mary was carried at home and abroad by a number of resourceful men. Charles Maitland, known to the Montagus since their time in Constantinople,[59] inoculated young Mary Montagu, aged three, in London in 1721. Later in the same year he became the inoculator concerned with the experiments sponsored by Caroline of Anspach, then Princess of Wales, and performed first on Newgate prisoners and orphan children, and eventually on her

[53] Singer, op. cit., note 49 above, p. 84.

[54] Fuller, op. cit., note 52 above, p. 176.

[55] Ibid., p. 93.

[56] Ibid., p. 118.

[57] In the manuscript of a book called 'The Angel of Bethesda', which for reasons which remain obscure was never published, Cotton Mather vividly summarized attitudes at the beginning of the eighteenth century in the following terms: "So few among the miserable Children of Men do now escape [smallpox], that the Enquirers after Causes have suspected the Original of this Malady to be some Venom connate with every Man (derived, they'l tell you, from the Maternal Blood unto him) which lies dormient and buried, until it be fired by Contagion, and then furiously breaking out from its unknown Lurking-Place, it mixes with the whole Mass of Blood, and makes the terrible Disturbance, and even Destruction, the Fear whereof holds Mankind in a very uneasy Bondage." See O. T. Beall, jr. and R. H. Shyrock, *Cotton Mather: first significant figure in American medicine* (Publications of the Institute for the History of Medicine, 1 ser., monographs V), Baltimore, Md., Johns Hopkins Press, 1954, pp. 127–234, see p. 160.

[58] Fuller, op. cit., note 52 above, p. 179.

[59] Charles Maitland (1668–1748) was a Scot who in 1717 was in Constantinople, serving as surgeon to the Embassy.

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own children, while Sir Hans Sloane lent the authority of the Royal Society to the enterprise.[60] The results obtained in these early years were analysed statistically, also under the auspices of the Royal Society, by James Jurin, whose data were instrumental in furthering the acceptance of inoculation in some quarters.[61]

It is during the trial inoculations, under royal sponsorship, that may be found the first documented use of pus taken from a patient with inoculated smallpox, rather than the natural disease, for further inoculation performed by Maitland. Genevieve Miller has pointed out that James Kirkpatrick has erroneously been credited with the introduction of this method, largely, it seems, due to successful self-advertisement.[62] On the other hand, Kirkpatrick should be remembered for upholding the suggestions of his erstwhile teacher, Boerhaave, that something remained after an attack of smallpox which prevented further attacks in the same individual: or, as Kirkpatrick put it, the frank disease "left some positive and material Quality in the Constitution" of the patient after recovery.[63] But such thoughts were not entertained by other writers in the eighteenth century, and the ideas of Boerhaave and of Kirkpatrick in this respect were not seminal for later theories of immunity.[64]

At the same time, the activities of Cotton Mather and of Zabdiel Boylston established the practice of inoculation in the American colonies during the severe epidemics in the 1720s, although, as elsewhere, savage controversy ensued.[65] From the middle of the eighteenth century the Suttons, father and sons, were developing their very successful system of inoculation. Among other practitioners who found it advantageous to copy the Suttons' system was Thomas Dimsdale; in 1768 he was invited to Russia to inoculate Catherine the Great, who in gratitude bestowed on him the title of Baron of the Empire.[66]

On the European continent, one name stands out in the history of variolation in the eighteenth century, as in the history of medical thinking: Angelo Gatti. Gatti was a Tuscan, born near Pisa in 1724; by the time he was forty, he had become an

[60] Maitland's account of the experimental inoculation of the Newgate prisoners is reproduced in facsimile in Dixon, op. cit., note 4 above, pp. 227–232.

[61] See Thomas Marmion, 'A forgotten chapter in the history of medical statistics (James Jurin on inoculation against smallpox)', *Med. Ill. (London)*, 1949, **3**: 266–270.

[62] Miller, op. cit., note 39 above, see p. 89.

[63] James Kirkpatrick, *The analysis of inoculation: comprising the history, theory and practice of it: with an occasional consideration of the most remarkable appearances in the small pox*, London, J. Millan, 1754, see p. 29.

[64] Miller, op. cit., note 39 above, see p. 263.

[65] In the early 1720s the printing-houses of Boston, Massachusetts, were kept busy with a succession of small volumes; a few titles serve to set the scene. W. Cooper, *A letter to a friend in the country, attempting a solution of the scruples and objections of a conscientious or religious nature, commonly made against the new way of receiving the small-pox*, Boston, S. Gerrish, 1721. John Williams, *Several arguments proving that inoculating the small pox is not contained in the law of physick, either natural or divine, and therefore unlawful*, Boston, J. Franklin, 1721. W. Douglass, *The abuses and scandals of some late pamphlets in favour of inoculation of the small pox; modestly obviated and inoculation further consider'd . . .*, Boston, J. Franklin, 1722. *A vindication of the Ministers of Boston, from the abuses and scandals, lately cast upon them, in diverse printed papers, by some of their People*, Boston, S. Gerrish, 1722.

[66] For details of the Suttons' careers, see D. Van Zwanenberg, 'The Suttons and the business of inoculation', *Med. Hist.*, 1978, **22**: 71–82; Dimsdale's exploits are described by W. J. Bishop in 'Thomas Dimsdale, M.D., F.R.S. (1712–1800) and the inoculation of Catherine the Great of Russia', *Ann. med. Hist.*, 1932, n.s. **4**: 321–338.

authority on the practice of variolation, had been brought to Paris from his chair of medicine at Pisa,[67] and was writing two volumes on smallpox inoculation[68] which both in their practical recommendations and their theoretical considerations are remarkable for their time. The fact that a number of authors have pointed out, in the present century, that Gatti is "largely forgotten", leaves the reader with a warm feeling of reassurance; Gatti is not, after all, to remain forgotten. Not only because of his considerable efforts on behalf of inoculation which paradoxically seem to have borne fruit rather more readily in other European countries than in his native Italy;[69] but first and foremost for his insight into the nature of the infection, and for his life-long search for ways and means of attenuating the virus, or what he called "weakening the variolous matter".[70] If this could be achieved, wrote Gatti, then no more flaws would remain in the art of inoculation.[71] He never quite accomplished his goal;[72] and he died just three months before Jenner finished his experiments with cowpox. There is no record of Gatti ever having been confronted with cowpox; but C. E. Daniëls in the late nineteenth century pointed out that Gatti's Dutch contemporary, and fellow-inoculator of French royalty, Theodore Tronchin,[73] when told of the apparent immunity to smallpox of milkers in Gloucestershire who had had cowpox, merely shrugged his shoulders and remarked: "How can they be so superstitious?"[74]

As for the nature of the infection in smallpox, Gatti expressed himself no less clearly than Fuller. Writing more than thirty years later, Gatti represented the more rational views held by those in the forefront of the medical profession in the latter half of the century of the Enlightenment. His two volumes mark the final demise of belief in the innate seed as the cause of smallpox;[75] he stated clearly his belief that the "variolous matter" was introduced into the organism from outside, and subsequently transmitted from human body to human body. Once introduced, it reproduced itself and multiplied indefinitely, but "its reproduction takes place only at the expense of a more or less severe disturbance of the organism".[76] Gatti pointed out

[67] Angelo Gatti (1724–1798) was Professor of Medicine at Pisa from 1755 to 1762; he moved to Paris in 1761.

[68] Gatti, op. cit., note 24 above.

[69] Gatti returned to his native Tuscany in the 1770s and is said to have been called to the Neapolitan Court to perform inoculations in 1778, but little is known of his later years, see A. C. Klebs, 'Die Variolation im achzehnten Jahrhundert', in K. Sudhoff and Georg Sticker (editors), *Zur historischen Biologie der Krankheitserreger*, Giessen, Verlag von Alfred Töpelmann, 1914, Heft 7. See also Andrea Oberti, *Per la storia della vaccinazione*, Pisa, Giardini, 1970.

[70] Gatti, *Réfléxions* . . ., 1764, op. cit., note 24 above, see pp. 82–83.

[71] ". . . il ne resteroit plus rien à désirer dans l'Art d'inoculer, si on pouvoit y parvenir, mais je ne connois aucun moyen d'obtenir cet affoiblissement", ibid.

[72] Klebs, op. cit., note 69 above, has pointed out that Gatti's method was in all probability derived from the Suttonian system of inoculation. His attempts to use attenuated inoculation material resulted in several cases in failure to produce immunity, see ibid., p. 40. Such failures were gleefully used as argument by the anti-inoculation lobby.

[73] Tronchin, like Matthew Maty who translated Gatti's works into English, was of French Huguenot descent. See Henry Tronchin, *Un médecin du XVIII^e^ siècle. Théodore Tronchin (1709-1781)*, Paris and Geneva, Plon-Nourrit, 1906.

[74] C. E. Daniëls, 'De kinderpok-inenting in Nederland', *Nederl. Tidjschr. Geneesk.*, 1875, 2.R., **11** (2): 17–223, see p. 55.

[75] For a discussion of the theory of the innate seed and its fate, see Miller, op. cit., note 39 above, pp. 242–246.

[76] Gatti, *Réfléxions* . . ., op. cit., note 24 above, p. 30.

that even very small quantities of infected material would produce specific diseases when introduced into the human body because of their ability to multiply once inside an otherwise healthy organism, and that this applied equally to the various specific "poisons" contained in "the pus of a pestiferous bubo, the saliva of a person suffering from rabies, the virus from a smallpox sufferer".[77] Gatti's attempts to "weaken the variolous poison" were well conceived, but not really successful. There were too many unknown factors, and occasionally Gatti's activities may have done his cause more harm than good.[78]

Gatti is said to have been a persuasive talker, and his published works were enhanced by the beguiling prose of André Morellet. In the intellectual climate of mid-eighteenth-century France, the attention of friend and foe alike ensured maximum publicity for his thoughts and ideas.[79] Less well known, but also interesting, views on attenuation and inoculation were held by the Dane, C. F. Rottböll, who had spent some months in Paris before the arrival of Gatti.[80] Like Gatti, Rottböll campaigned against the unnecessary and often harmful "preparation" of patients prior to inoculation;[81] and he also believed that the matter used for inoculation could eventually be attenuated by passage through the organism. He even offered a hypothesis concerning the mechanism of attenuation. According to Rottböll, this process was taking place in the blood, where the "sharp and biting particles of the smallpox poison" were weakened by association with fatty particles.[82] Rottböll also made interesting comments on the danger of transmitting other diseases, such as syphilis, with the material used for inoculation.[83]

[77] Ibid., p. 31.

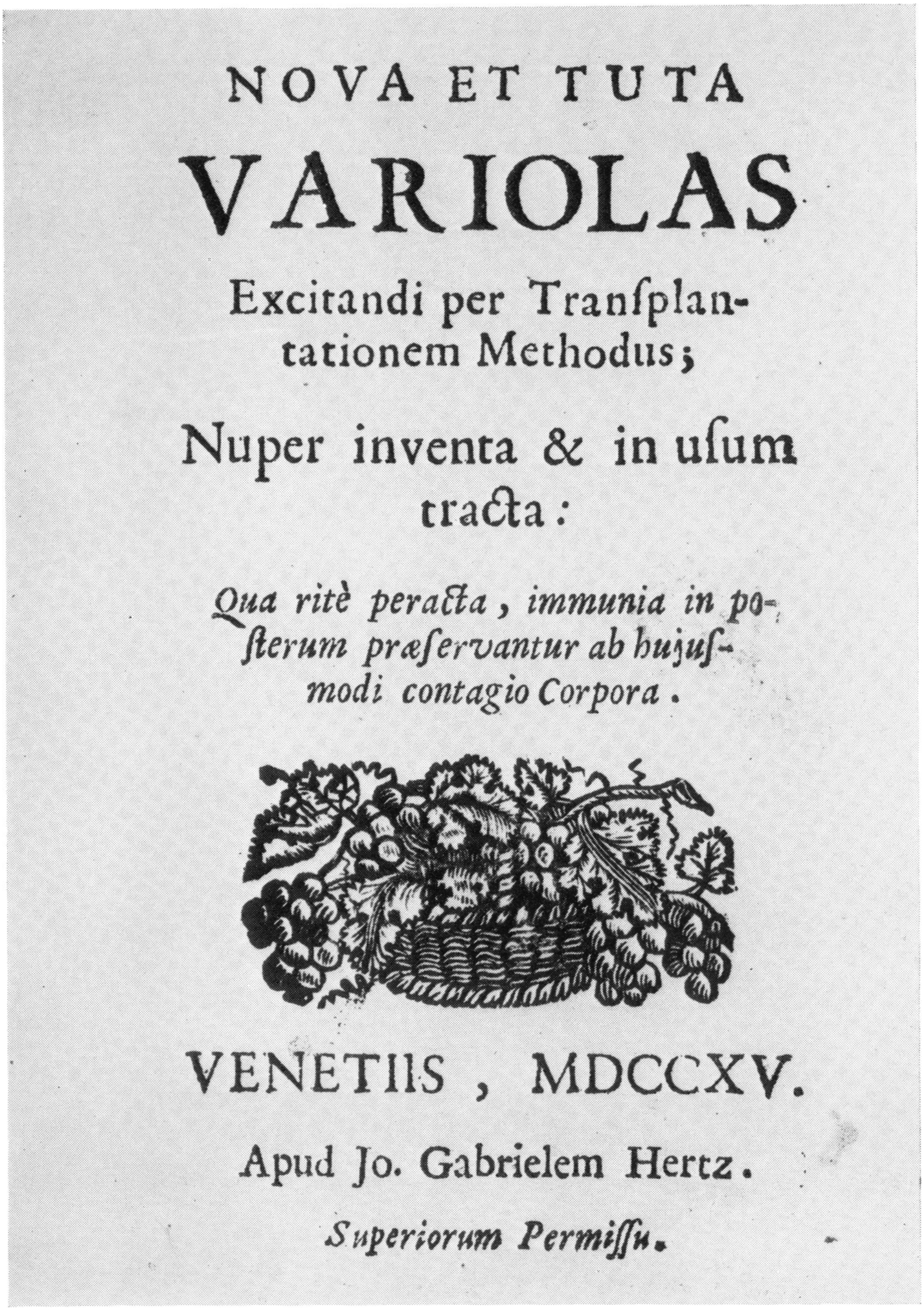
[78] Even Tronchin was moved at one time to criticize Gatti for a carelessness which encouraged the opposition, see Miller, op. cit., note 39 above, p. 232.

[79] André Morellet, or l'abbé Morellet (1727–1819), was one of the Encyclopédistes, Sorbonne-educated, friend of Diderot, d'Alembert, and Turgot. The *Nouvelle biographie generale*, Paris, Firmin Didot, 1865, lists among his published works "*Réfléxions sur les préjugés qui s'opposent aux progrès et à la perfection de l'inoculation*, trad. de l'italien de M. Gatti, 1764." Neither the *Réfléxions* nor the *Nouvelles réfléxions* (note 24 above) mention a translator on the title-page or in the preface; but at the end of *Réfléxions* appears a brief note: "P. S. Je crois devoir avertir, qu'Etranger en France, j'ai emprunté le secours d'un ami pour écrire avec plus de correction dans une langue qui ne m'set pas assez familière" (p. 239).

[80] Klebs, op. cit., note 69 above, speculated on contacts made and influences received by Rottböll (1727-1797) during his travels in Holland, France, and Italy during the years 1757-1760. In fact Rottböll undertook this journey to study botany abroad, having spent some months previously with Linnaeus in Uppsala, in order to qualify for the teaching of botany in the University of Copenhagen. After the publication of "Forsøg . . ." (note 81 below), Rottböll's subsequent output consisted of botanical papers. One contact quoted by Rottböll was a certain "Dr. Gandini of Genna" [*sic*], who believed that severe cases of smallpox were caused by the disturbance created by the reaction between the external contagion and the innate seed, and that by introducing the "fully developed inoculation material" it was possible to avoid this unfortunate collusion taking place within the body of the patient. Rottböll quotes Gandini only to repudiate his thesis, commenting that it "reintroduces the antiquated belief in effervescence and fermentation, which has long been happily buried" (p. 469); clearly Rottböll had accepted the more enlightened concept of simple contagion and rejected the innate seed.

[81] Christen Friis Rottböll, 'Forsøg til en nye Grund-Laere om Koppernes Indpodning', *Skrifter, Kjøbenhavnske Selskab af Laerdoms og Videnskabers Elskere* [Videnskabernes Selskab], 1761–1764, 9: 449–491.

[82] Ibid., pp. 474–475; Rottböll subscribed to a general theory that all potentially evil and dangerous products of the liver, kidneys, colon, and rectum were rendered harmless by the body's reservoirs of "oil and fatty particles". [83] Ibid., pp. 482–483.



NOVA ET TUTA

VARIOLAS

Excitandi per Tranſplan-
tationem Methodus;

Nuper inventa & in uſum
tracta:

*Qua ritè peracta, immunia in po-
ſterum præſervantur ab hujuſ-
modi contagio Corpora.*

VENETIIS, MDCCXV.

Apud Jo. Gabrielem Hertz.

Superiorum Permiſſu.

Figure 1.
Title-page of Pylarino's treatise on inoculation. (*Reproduced by courtesy of the Wellcome Trustees.*)

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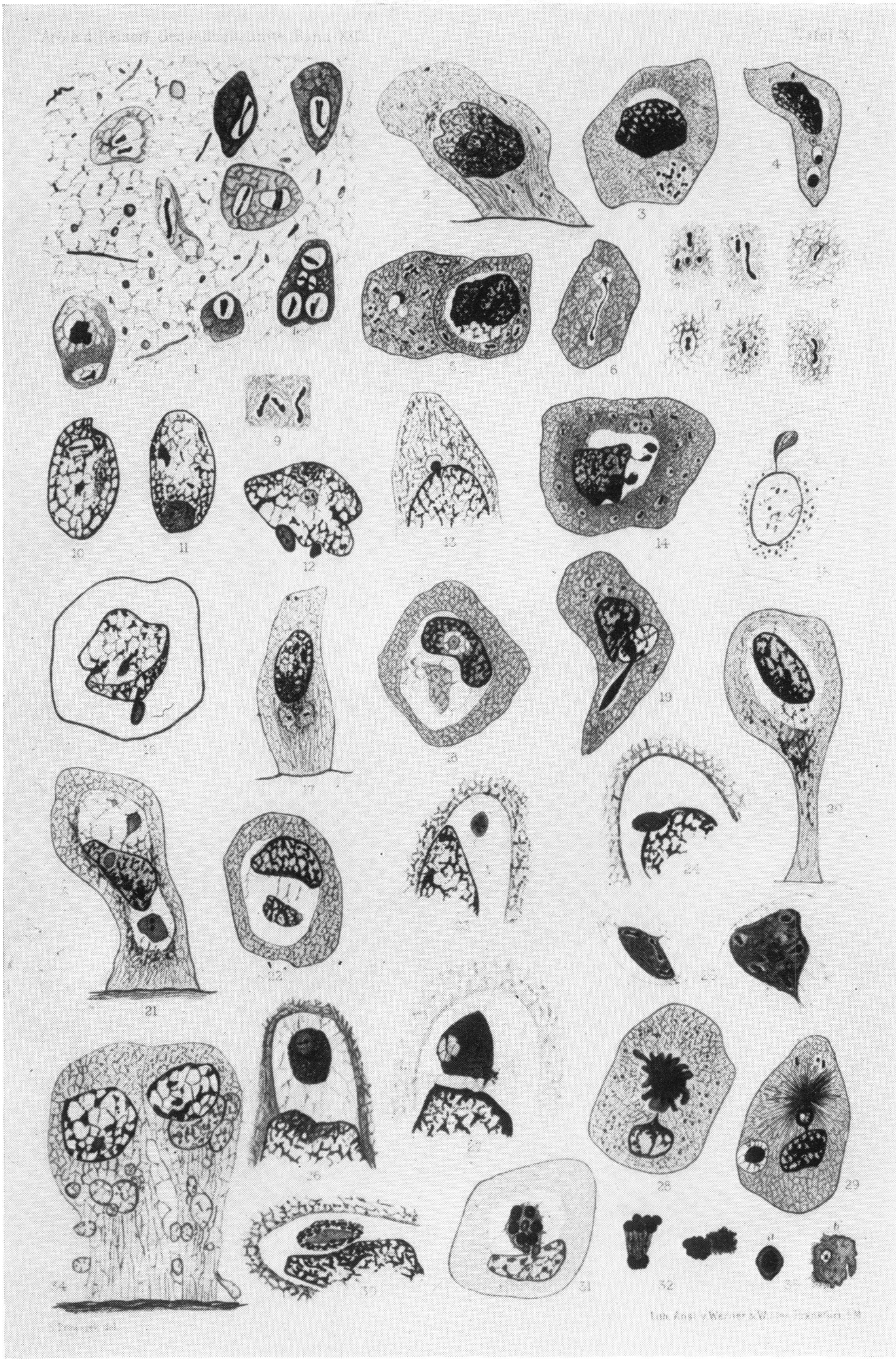

Figure 2.
Von Prowazek's meticulous diagram of his microscopical observations on vaccinia material (1905), including Guarnieri bodies. (*Reproduced by courtesy of the Royal Society of Medicine.*)

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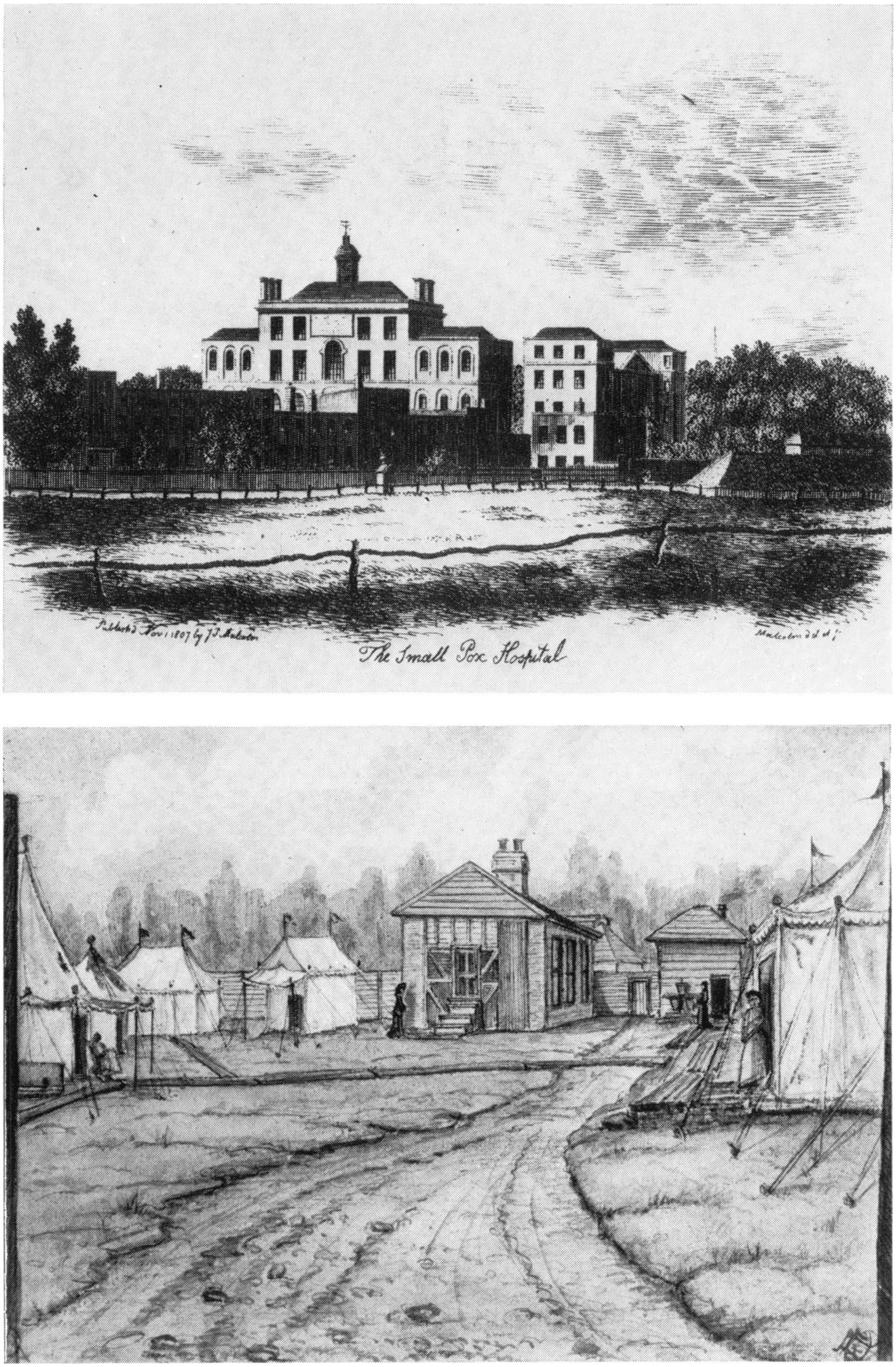

Figure 3.
The St. Pancras smallpox hospital: (*top*) in 1807, engraving by J. P. Malcolm; (*bottom*) tents and huts in the hospital grounds during the 1880–81 outbreak following which a Royal Commission was established to examine "the peculiar arrangements in London" (see Dixon, op. cit., footnote 4, pp. 365–367), watercolour by Dr. Frank Collins, 1881. (*Reproduced by courtesy of the Wellcome Trustees.*)

By the late 1750s variolation had become a well-known, if by no means a universally accepted practice. Some physicians who believed in its advantages began to suggest that a similar method might be developed to avoid, if possible, the severe pulmonary complications sometimes developing in naturally transmitted measles. Hektoen has reviewed these early endeavours;[84] they seem to have been of little avail except in the prejudiced estimation of their initiators. The report published by Francis Home in Edinburgh in 1759 may well have been the result of work directly derived from suggestions made by Alexander Monro (secundus) two years before.[85] Monro, drawing the obvious parallel with variolous inoculation, proposed the application of matter from pustules or spots to a small incision; Home found that in actual practice there was only a negligible amount of "matter" to be had from the measles rash. Instead he used blood "from the most feverish patients", taken "when it contained the morbific matter in the highest state of acrimony".[86] Less than ten years later, the recommended source of measles "matter" for inoculation had become "the watery humour that stands in the eyes of persons ill of the measles about the time of the crisis".[87]

Interest in the eruptive fevers during this period also produced, in 1767, the first clinical description of chicken-pox as a separate entity distinct from smallpox. Written by the elder Heberden[88] it is a lucid and definitive account. Its appearance was prompted, Heberden points out, by the danger of this relatively mild complaint being confused with smallpox, and thus lulling its victims into a false sense of security in the belief that they would henceforth be immune to smallpox.[89] In fact, there can be little doubt that varicella had been known for centuries, and it may have been described as a mild form of smallpox not only by Rhazes and Avicenna, but also by Indian writers.[90] In the sixteenth century it was referred to as "crystalli", while the common name of "chicken-pocks" had long been in use in rural England when Richard Morton in the seventeenth century bestowed it on what he called "*variola benigna*" as opposed to "*variola maligna*".[91] Thomas Fuller in 1730 described separately what he called "Rittelen or Chicken-Pox"[92] and "The Crystals";[93] but he made no very clear distinction between the two brief accounts, although he certainly treated both diseases as quite distinct from smallpox and measles.

German measles, even milder and considered worthy of only scant attention until its sinister implications began to be known during World War II, was described as an entity distinct from *scarlatina* by W. G. Maton in 1815,[94] and by Wagner in Germany

[84] Ludvig Hektoen, 'Experimental measles', *J. infect. Dis.*, 1905, **2**: 238–255.
[85] Ibid., p. 238.
[86] Ibid., p. 239.
[87] Current opinion favours the view that virus could be isolated from this source.
[88] W. Heberden, 'On the chicken-pox', *Med. Trans. Coll. Phys. Lond.*, (paper read at the College 11 August 1767), 1768, **1**: 427–436.
[89] Ibid., pp. 427–428.
[90] Ebstein, op. cit., note 7 above.
[91] Ibid., see p. 187.
[92] Fuller, op. cit., note 52 above, p. 161.
[93] Ibid., p. 163.
[94] W. G. Maton, 'Some account of a rash, liable to be mistaken for scarlatina', *Med. Trans. R. Coll. Phys.*, 1815, **5**: 149–165.

in 1829.[95] The name *rubella* was suggested, as an alternative to the German *Rötheln,* by Henry Veale in 1866.[96] None of these authors proffered opinions concerning the nature of the contagion in the diseases they were describing, and only Fuller left us a few pages comparing different eruptive fevers which we now know to be of viral origin.[97] It is interesting though to note that when Kirkpatrick, in 1745, observed that the ability to produce lasting immunity seemed "almost peculiar" to smallpox and measles, he added a footnote to the effect that this might also apply to "swine pox and chicken pox" and a number of other diseases which occurred only once in a person's lifetime, adding that "we scarcely consider them Diseases, since Physicians are very seldom called in to them".[98]

In his trenchant passages on the nature of smallpox infection, Gatti had alluded to the infectious agent as a specific, self-producing poison. When he referred to the "virus", the term took on the meaning of the lymph contained in vesicles. It was in this same sense that Edward Jenner used the word "virus" when he published his famous treatise[99] in 1798, the year of Gatti's death; but in their approach to the problem of smallpox, the two men were entirely different. Gatti, the successful inoculator, searched for more than thirty years deliberately, albeit in vain, for a satisfactory, reproducible method for attenuation of the pathogen of smallpox. In the absence of an adequate theoretical background, his cerebral approach could not provide a solution to the problem of producing immunity without risk of serious disease. Jenner's forte was his keen powers of observation; his luck was that his was a country practice in an English county where cowpox was endemic.[100]

Nor was Jenner's by any means the first observation of the transmission of cowpox to man, or of its prophylactic qualities. The story of farmer Jesty who attempted to protect his family with cowpox during an epidemic of smallpox is well known.[101] Théodore Tronchin's reaction to the tale of smallpox prevention in Gloucestershire has been quoted above. That was in 1754, when Edward Jenner was five years old; and although cowpox was unknown in some parts of the British Isles, it was as common in parts of Europe as it was in Gloucestershire;[102] but little evidence of the extent of knowledge or of attitudes to this knowledge before Jenner has been preserved. George Pearson, in *An inquiry concerning the history of the cowpox,* appended a letter from a Thornbury surgeon, a Mr. Fewster, who, inoculating at Buckover under the auspices of the Suttons in 1768, came across the immunity produced by

[95] [–] Wagner, 'Die Rötheln als für sich bestehende Krankheit', *Litt. Ann. ges. Heilk.*, 1829, **13**: 420–428.

[96] Henry Veale, 'History of an epidemic of Rötheln, with observations on its pathology', *Edinb. med. J.*, 1866, **12**: 404–414.

[97] Fuller, op. cit., note 52 above, pp. 125–163; although this also includes certain eruptions of non-viral origin, among them "spots from flea-bites".

[98] Kirkpatrick, op. cit., note 63 above, see footnote p. 51.

[99] Edward Jenner, *An inquiry into the causes and effects of the variolae vaccinae,* London, Sampson Low, 1798.

[100] See Dixon, op. cit., note 4 above, chapter 12.

[101] Ibid.

[102] In the early nineteenth century, indigenous cowpox lymph was used both in France (environs of Paris) and in Italy (Lombardy); see S. Monckton Copeman, *Vaccination: its natural history and pathology,* London, MacMillan, 1899, p. 69.

cowpox and "communicated this fact to a medical society".[103] Also in Thornbury, Drs. Rolph and Grove made similar observations; but they all saw the result of cowpox infection more as an impediment to variolation than as a possible alternative. Pearson himself had been told by John Hunter of Jenner's observations in the late 1780s, and claimed that he had mentioned them in "every course of lectures" on the subject of smallpox which he had delivered since.[104] He also recorded a conversation he had had with Sir George Baker, after the publication of Jenner's experiments, in which Sir George "observed, he had been informed of the fact, in some papers, on the Cow Pox, *communicated to him many years ago* [my italics], but that as the statement did not then obtain credit, it was not published . . .".[105] Perhaps the best claim to have preceded Jenner belongs to the Dane, Peter Plett, some-time tutor to dairy farmers in Schleswig-Holstein, who in 1790 reported to the medical faculty of the University of Kiel on "Four years of observations on cowpox and smallpox", and suggested preventive inoculation of cowpox. His report was ignored, as was a second one, made in 1792 after he had himself successfully vaccinated a number of children.[106]

Thus the development of Jenner's method of vaccination was the logical culmination of years of observation and accumulated facts, rather than a sudden discovery. Jenner's great merit was perseverance and the ability tirelessly to publicize his ideas, in spite of discouraging setbacks. Many things went wrong, especially since the practice of establishing vaccination clinics within working smallpox hospitals provided endless opportunities for contamination of the lymph used for vaccination. The distressing accidents fed the increasingly acrimonious debate, which in Britain in the nineteenth century polarized the medical community and lasted longer than elsewhere in Europe, a fact which may have been responsible for the late introduction of revaccination.[107]

While the extent and viciousness of the vaccination controversy to some extent precluded more constructive thinking on the nature of the agents of variola and vaccinia in England, progress was being made elsewhere during the nineteenth century. By mid-century, dramatic improvements had been made to the light microscope,[108] and botanists, physiologists, anatomists, and pathologists eagerly explored the new dimensions which had been made available. Vaccinia lymph was one of many popular objects for scrutiny. G. A. F. Keber was an early exponent of the new school of investigative microscopy. A practising physician, Keber used the more powerful

[103] George Pearson, *An inquiry concerning the history of the cowpox, principally with a view to supersede and extinguish the smallpox*, London, J. Johnson, 1798, see p. 102.

[104] Ibid., p. 6.

[105] Ibid., p. 7.

[106] See Ida Rich, 'Cowpox inoculation suggested to a medical faculty in 1790', *XVth Int. Congr. Med.*, Madrid, 1957, pp. 473–476.

[107] Revaccination was already recognized as being desirable on the continent of Europe within Jenner's lifetime. First attempts to make it compulsory were restricted to the armed forces, in Germany (Württemberg) in 1829, in Denmark 1835–36; in France the Académie des Sciences in 1838 offered prizes for the best essays on 'The necessity of revaccination'. See Julius Petersen, *Kopper og Koppeindpodning*, Copenhagen, F. Hegel, 1896, pp. 282–292.

[108] Giovanni Battista Amici (1786–1863) introduced the oil-immersion technique in 1840, and made major improvements in compound-microscope design; see Vasco Ronchi, 'Giovan Battista Amici's contribution to the advances of optical microscopy', *Physis*, 1969, **11**: 520–533.

microscopes to study general physiological phenomena in the lower animals, which lent themselves more easily to experimentation. Having published a classic series of studies of the nervous and reproductive systems of molluscs, he turned in the last few years of his life[109] to the study of vaccinia lymph. Regrettably, the paper he published in 1868 in *Virchow's Archiv* contains no illustrations;[110] but when he observed "molecules as fine points of barely measurable dimensions" he may conceivably have seen the same elementary bodies which Buist was to stain and depict in 1886.[111]

Keber had ascertained that even lymph diluted with water was able to induce the formation of true pustules in his patients, and it led him to suggest that it might be the cell-like formations suspended in the lymph rather than the liquid itself which were the active constituents. To test this hypothesis Keber designed a primitive filter experiment, with the means at his disposal. He filtered small amounts of fresh vaccinia lymph through "Swedish filter paper", and used the filtrate for inoculation. To his surprise, he found that the filtrate induced pustules, suitable for re-inoculation, in susceptible individuals. Keber re-examined the active filtrate under the microscope, and found that although the larger particles ("Körnchenzellen") had been retained by the filter, a number of "nuclei and molecules"[112] had passed through the filter with the liquid. Keber made his observations on lymph taken straight from the pustules of his patients undergoing vaccination. More than half a century earlier, Luigi Sacco in Milan had recorded microscopical observations of vaccinia lymph of varying degrees of maturity (six days, eight days, etc.). Sacco's experiments were well planned and executed; but his instruments and techniques were primitive and his results of minor importance, except perhaps as a notable first in painstaking microscopic examination of clinical material.[113] But by 1868, when Keber's observations were published, the deliberate search for agents of infectious disease was fuelled by a new-found sense of reality. The studies of anthrax had moved, during the 1860s and 1870s, from Davaine's at first tentative but over the years increasingly confident experiments, to culminate in the definitive works of Koch[114] and of Pasteur and Joubert,[115] which not only solved the question of the aetiology, but which also

[109] Gotthard August Ferdinand Keber was born in 1816, studied in Königsberg and Berlin, and eventually became *Kreisphysikus* with the title of *Regierungs-Medicinalrath* in Danzig, where he died in 1871.

[110] G. A. F. Keber, 'Ueber die mikroskopischen Bestandtheile der Pocken-Lymphe', *Virchows Arch. path. Anat. Physiol.*, 1868, **42**: 112–128. At the end of the paper Keber notes that he has deposited some illustrations with the editor, but they were aparently never published.

[111] (a) John Brown Buist, 'The life-history of the micro-organisms associated with variola and vaccinia', *Proc. R. Soc. Edinb.*, 1886, **13**: 603–620. (b) J. B. Buist, *Vaccinia and variola, a study of their life history*, London, J. & A. Churchill, 1887.

[112] Keber, op. cit., note 110 above, p. 118.

[113] Luigi Sacco, *Trattato di vaccinazione, con osservazioni sul giavardo e vajuolo pecorino*, Milan, Mussi, 1809. Luigi S. Sacco (1769–1836) was a great champion of Jenner's vaccination in Italy, where he used local cowpox material from sources in Lombardy (cf. Copeman, op. cit., note 102 above, p. 69). His interests were catholic, including also acupuncture, disinfectants, malaria control, and the introduction of sugar beet and camellias into Italy.

[114] Robert Koch, 'Die Aetiologie der Milzbrand-Krankheit, begründet auf die Entwicklungsgeschichte der *Bacillus anthracis*', *Beitr. Biol. Pfl.*, 1876, **2**: 277–310.

[115] [L.] Pasteur and [J.] Joubert, 'Étude sur la maladie charbonneuse', *C.r.hebd. Séanc. Acad. Sci., Paris*, 1877, **84**: 900–906.

laid a solid foundation for the new discipline of bacteriology. At the same time, for these studies were developed the tools and the methodology which by the end of the century had spawned yet another concept: that of filterable viruses.

Keber declared himself surprised when he found the filtered vaccinia lymph to be infective. Already Davaine had ingeniously demonstrated the inability of the anthrax bacillus to pass through the guinea pig placenta, a most efficient natural membrane filter, in 1863.[116] From 1870 onwards, Edwin Klebs and his associates Tiegel and Zahn developed unglazed white clay cells as a means of bacteriological filtration,[117] and in 1877 Pasteur introduced plaster of Paris filters in anthrax research.[118] But long before that, in the same year Keber recorded his filtration of vaccinia lymph through "Swedish filter paper", a study of the nature of vaccinia lymph had been presented to the Académie des Sciences in Paris by Claude Bernard, on behalf of a remarkable and versatile man, J.-B. A. Chauveau.

At this time, Chauveau was in charge of the departments of anatomy and physiology at the veterinary school at Lyons.[119] During his first fifteen years at Lyons, from 1848 to 1863, Chauveau's work reflected the twin disciplines of his department. He wrote a comparative anatomy of domestic animals; and with Marey and Faivre he made fundamental contributions to the development of intracardiac cardiography.[120] Then, in 1863, the French Academy of Medicine took up the question of the origin of Jenner's cowpox vaccine. The problem had exercised the minds of a number of people since the beginning of the nineteenth century. Jenner himself had inclined to the theory that cowpox was the bovine equivalent of the so-called "grease" of the horse, and attempts had been made to transmit it to cattle and use the lymph produced for human vaccination. Raised by Bouley, the subject soon dominated many successive sessions of the august Académie de Médecine.[121] At the centre of the ensuing argument was the question of the relationship between variola and vaccinia, and of whether it was possible to produce the latter by passage of the former through certain animals.

The problem caught the imagination of Chauveau; in his mid-forties, with distinguished work in anatomy and experimental physiology to his credit, he turned to experimental pathology. Chairing a committee established by the Society for Medical Science in Lyons, he began a series of experiments aimed at determining the inter-

[116] C. Davaine, 'Nouvelles recherches sur la nature de la maladie charbonneuse connue sous le nom de "sang de rate"', ibid., 1864, **59**: 393–396.

[117] E. T. Tiegel, 'Die Ursache des Milzbrandes', *KorrespBl. schweizer Ärzte*, 1871, **1**: 275–280.

[118] [L.] Pasteur [and J. Joubert], 'Charbon et septicémie', *Bull. Acad. Méd.*, 1877, 2e ser., **6**: 781–798, p. 786. The work was also published elsewhere (*C.r.hebd. Séanc. Acad. Sci., Paris*, 1877, **85**: p. 61 and pp. 101–105); at the Académie de Médecine the report was delivered in the form of a talk by Pasteur.

[119] Jean-Baptiste Auguste Chauveau (1827–1917), after graduating from the veterinary school at Alfort, carried out his main research at its counterpart at Lyons until he went to Paris in 1886 as Inspector General of the Veterinary Schools and Professor of Comparative Pathology at the Museum of Natural History.

[120] See J. Bost, 'A propos du registre du laboratoire de Chauveau (Mars-Novembre 1861): l'histoire des premiers enregistrements cardiographiques', *Hist. Sci. méd.*, 1974, **8**: 595–626.

[121] See G. Ramon, 'Hommage à Jean-Baptiste Auguste Chauveau', *Bicentennaire de l'Ecole Nationale Vétérinaire de Lyon* (25–26 mai 1962).

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relationship between variola and vaccinia. In a classic study, the commission found that inoculation with variola did not produce cowpox in cattle, nor horsepox in horses. Among the published conclusions is also the laconic sentence: "Transmitted to man, it [variola passed through bovines] produces variola". Some authors who have later referred to the report in laudatory terms have studiously ignored the experiments on which this statement was based. In fact, a total of seven children were inoculated with variola which had been passed through cattle and horses; two developed confluent smallpox, the others the discrete but characteristic form.[122] Less than three months later Chauveau presented at the Académie de Médecine what amounted to an apologia for these experiments, referring to the "heavy responsibility" assumed by the commission in carrying out the study, and "in particular the experiments involving children".[123] The Lyonnaise committee certainly seems to have got off lightly when one considers the concern later aroused over yellow fever experiments.[124]

Three years later Chauveau had completed a detailed examination, published in the proceedings of the Académie des Sciences, of the theory of contagion and infection. It was preceded by three papers on the nature of virus, exploring the properties of what Chauveau called the "virulent principle" of vaccinia, variola, and glanders. Like Keber, Chauveau was attempting to learn about the nature of the agent by assessing the activity of different fractions of the lymph. Instead of filtration, Chauveau used diffusion, showing that none of the three agents investigated diffused from the lymph into a superimposed layer of water, and that consequently they could not be dissolved substances.[125] Hence, in spite of the difference between, on the one hand, diseases such as rabies, syphilis, and vaccinia, which are transmitted directly only in very special circumstances, and, on the other hand, those which like variola and foot-and-mouth disease appear to spread freely through the surrounding atmosphere, the disease agents were, in all of the cases examined, to be found, in diffusion experiments, in the fraction containing solid particles. Chauveau saw his results as a complete rejection of the suggestion that disease agents might be divided into "*virus fixes*" and "*virus volatils*", and concluded that the activity in virulent lymph, be it from vaccinia, variola, or glanders, resides in suspended particles. Chauveau called them *corpuscules élémentaires* or *granulations élémentaires*—and thus introduced the term which von Prowazek revived in 1905,[126] and which is still in use as "elementary bodies".

Separation by diffusion had been used in England at about the same time to analyse the constituents of liquids obtained from animals suffering from what was to turn

[122] [A.] Chauveau, 'Recherches expérimentales de la Société des sciences médicales de Lyon sur les relations qui existent entre la variole et la vaccine', *Bull. Acad. Méd.*, 1865, **30**: 808–816, see pp. 814–815.

[123] See G. Ramon, 'Des rapports de la vaccine et de la variole', *Biol. med.*, 1962, **51**: 19–41, p. 27.

[124] See William B. Dean, 'Walter Reed and the ordeal of yellow fever experiments', *Bull. Hist. Med.*, 1977, **51**: 75–92.

[125] A. Chauveau, 'Nature du virus vaccin. Determination expérimentale des éléments qui constituent le principe actif de la sérosité vaccinale virulente', *C.r. hebd. Séanc. Acad. Sci., Paris*, 1868, **66**: 289–293.

[126] S. von Prowazek, 'Untersuchungen über die Vaccine', *Arb. K. Gesundhamt.*, 1905, **22**: 535–556.

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out to be another virus disease: cattle plague, or rinderpest.[127] For this purpose Burdon-Sanderson used parchment paper, and reached the same conclusion as Chauveau in the above cases. In 1868 Burdon-Sanderson visited Chauveau in Lyons, and a certain amount of collaboration ensued; returning to London, Burdon-Sanderson improved the diffusion method by modifications to the apparatus used.[128]

Pasteur, who at the time was involved in the study of silkworm disease but had not yet turned his attention to human pathogens, admired the clear design and elegant execution of Chauveau's studies, and said so.[129] More than ten years later, when his own work on the development of vaccines had increased his confidence and given added weight to his opinions in the area of human infectious disease, he again expressed his support for Chauveau's work on vaccinia and variola in the Académie de Médecine, and was challenged to a duel for his pains by an irate octogenarian, one Jules Guérin.[130] The year was now 1880, and the understanding of micro-organisms and of their role in pathogenesis had advanced very considerably since the publication of Chauveau's earlier studies. A number of disease agents had been seen under the microscope in the laboratories of Koch and of Pasteur, had been grown in culture, and been unequivocally linked with their respective diseases according to Koch's postulates.[131] Armed with such new insight, Pasteur was beginning to be able to control some of these diseases by the development of vaccines.[132]

Increased knowledge of the nature of pathogens was accompanied by slowly improving possibilities of preventing epidemic outbreaks of certain infections. By the late nineteenth century, hopes of effective control of infectious disease had progressed from the vague and wistful suggestion by Gatti concerning the attenuation of smallpox virus by passage through "a number of bodies", via Jenner's stroke of luck, and Chauveau's bold experiments to Pasteur's deliberate attenuation of chicken

[127] Cattle plague was a major problem to cattle industries in Britain and Europe throughout the nineteenth century. In Britain, the authorities ignored the preventive measures advocated by John Gamgee in 1865 with disastrous results; towards the end of the century strenuous efforts were being made to develop a vaccine, with extensive field-work being carried out in South Africa, see for example R. Koch, *Reise-Berichte über Rinderpest, Bubonenpest in Indien und Afrika, Tsetse oder Surrakrankheit, Texasfieber, tropische Malaria, Schwarzwasserfieber*, Berlin, Julius Springer, 1898, see pp. 7–23.

[128] J. Burdon-Sanderson, Introductory report on 'The intimate pathology of contagion' in Appendix to *12th Annual Report of the Medical Committee of the Privy Council*, London, Eyre & Spottiswoode, 1869. In 1898 Copeman (op. cit., note 102 above), probably with a slip of memory because of later developments, credited Burdon-Sanderson with having also used "a layer of unglazed porcelain" as a filter on this occasion.

[129] See Ramon, op. cit., note 123 above, p. 28.

[130] Ibid., p. 31. Jules René Guérin was born in Belgium in 1801, and died in 1886. His interests were mostly in orthopaedic subjects, congenital malformations, rachitis, etc. On this occasion he claimed that it was already an established fact, formulated first by himself, that vaccinia was "variola of animals (cowpox and horsepox) inoculated into man and humanized by successive transmissions", and declared that further discussion was pointless.

[131] The postulates and their fate over the years, and in the light of new knowledge of viral diseases, have been examined by A. S. Evans in 'Causation and disease: the Henle-Koch postulates revisited', *Yale J. Biol. Med.*, 1976, **49**: 175–195.

[132] Beginning with chicken cholera vaccine (1880), Pasteur moved via anthrax vaccination (1881) to his spectacular success with post-exposure rabies prophylaxis (1885). For further details of this development see *Med. Hist.*, 1977, **21**: pp. 22–23.

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cholera cultures by exposure to atmospheric oxygen and controlled heat.[133] After the successful development of vaccines against anthrax[134] and chicken cholera, Pasteur turned to the much more difficult problem of post-exposure prophylaxis against rabies, and was able eventually to produce a vaccine in spite of the prevailing ignorance of the identity of the pathogen involved. By 1885, when rabies vaccine was first used prophylactically in man, attempts had been made to control smallpox epidemics first by variolation and later by vaccination for the better part of two centuries. Still the agents of smallpox and of cowpox remained almost as much of an enigma as the rabies pathogen.

Almost, but not quite. Certain microscopical observations had been made. Keber had seen "nuclei and molecules" in the filtrate of vaccinia lymph which proved to be still active. In the years following his observations, techniques for the staining of histological material had been greatly improved,[135] and Robert Koch in particular had developed a series of stains for bacteriological samples. In 1886, John Brown Buist[136] presented to the Royal Society of Edinburgh an account of a study he had carried out in the surgical laboratory at the university. He called his paper 'The life-history of the micro-organisms associated with variola and vaccinia'. Buist had been able to fix and stain (with Koch's aniline methyl-violet stain) samples of lymph from variola and vaccinia pustules, and his method had allowed him to see what he called "spores of micrococci", but which were almost certainly elementary bodies of the pox viruses. Buist quoted the results obtained previously by Keber, Chauveau, and Burdon-Sanderson; apparently he misread certain passages in Keber's account, since he tells us that the filtrate of Keber's lymph produced no pustules upon inoculation.[137] Having discussed his own impeccable microscopical observations, Buist concluded with a rather ingenious misinterpretation, including a reference to, presumably, Pasteur's recent work on vaccines. He wrote: "My observations appear to show that what is called 'attenuation of a virus' may be explained by spore-production. Are not the perfect vaccine materials for infective diseases to be found in the spores of the micro-organisms which are their exciting causes?"[138]

Thus Buist's microscopical examinations of vaccinial and variolar lymph led him to believe that the pathogens were spore-forming micrococci. In distant Italy, in another ancient university with a time-honoured medical school, Guiseppe Guarnieri[139] came to a different conclusion a few years later; he also discovered another manifestation characteristic of the pox viruses. Guarnieri also made comparative studies of vaccinia and variola, but he was not content to examine only the lymph from the

[133] L. Pasteur, 'Sur le cholera des poules. Études des conditions de la non-récidive de la maladie et de quelques autres de ses caractères', *Bull. Acad. Méd.*, 1880, 2e ser., **9**: 390–401.

[134] [L.] Pasteur, [C.] Chamberland and [E.] Roux, 'Le vaccin du charbon', *C.r. hebd. Séanc. Acad. Sci., Paris*, 1881, **92**: 666–668.

[135] See H. J. Conn, 'The development of histological staining', *Summit, N. J., Ciba Symp.*, 1946, **7**: 270–300.

[136] Buist, op. cit., note 111 (a) above.

[137] Buist, op. cit., note 111(b) above, see p. 55.

[138] Buist, op. cit., note 111 (a) above, p. 618.

[139] Guiseppe Guarnieri (1856–1918) was Professor of Pathology at Pisa, in the old medical school which still uses part of its original fourteenth-century buildings, across the piazza from the leaning tower.

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pustules. Interested in the pathological anatomy of the lesions, Guarnieri examined microscopically specimens from patients who had died of smallpox (regretting that his material was "of necessity collected only several hours after death had occurred.")[140]

Describing his observations, Guarnieri left us the first record of inclusion bodies in vaccinia and variola. For his experiments with vaccinia, he found the pustules produced by inoculation in the mammary region of ewes and rabbits unsatisfactory, and he proceeded to use what was to become the classic tissue for histological study of this type of inclusion body, namely the rabbit cornea.[141] Drawing on his detailed and meticulous observations of the epithelial changes in the infected rabbit cornea, and relating these observations to the ones made on post-mortem material from fatal cases of variola in man, he drew his conclusions. While acknowledging the possibility of future improved studies of the morphology and biology of the responsible "micro-organism",[142] Guarnieri had few reservations in announcing his verdict. He described, with suitable illustrations, what he considered to be the protozoa which he identified as the aetiological agents responsible for variola and vaccinia, respectively. In Guarnieri's preparations, they appeared to be amoeboid, undergoing characteristic changes although, he wrote "Their amoeboid movements . . . are sluggish, much slower than those observed in malarial amoebae in human red cells". Pending further studies, Guarnieri named the protozoa he held responsible *Citoryctes vaccinae* and *Citoryctes variolae,* alluding to what he considered their characteristic histopathological invasion of the cells of the protoplasm.[143] The protozoal misinterpretation of viral inclusion bodies was to persist well into the 1920s in one form or another;[144] but the valiant effort made by Guarnieri has been acknowledged in the linking of his name to the inclusion bodies of variola and vaccinia to this day.

Guarnieri also strengthened his case by allusion to similar "protozoal parasites" associated with a disease with similar epithelial manifestations in pigeons, and originally described by a colleague of his at Pisa, one Sebastiano Rivolta,[145] and, in 1873, by von Bollinger in Zürich.[146] Known as *epithelioma contagiosum,* this disease played a prominent role in much early research in the late nineteenth and early twentieth centuries; as fowl pox it has continued to be in the forefront of virus research later in the twentieth century.[147] It was the abiding interest of another

[140] G. Guarnieri, 'Ricerche sulla patogenesi ed etiologia dell'infezione vaccinica e vaiolosa', *Arch. Sci. med.*, 1892, **16**: 403–423.

[141] Ibid., pp. 411–413.

[142] Ibid., pp. 418–419.

[143] Ibid., p. 422.

[144] E.g., for rabies, see C. Levaditi, S. Nicolau and R. Schoen, 'Recherches sur la rage', *Annls Inst. Pasteur, Paris,* 1926, **40**: 973–1068; for tobacco mosaic virus, see R. Nelson, 'The occurrence of protozoa in plants affected with mosaic and related diseases', *Tech. Bull. Mich. (St. Coll.) agric. Exp. Stn,* 1922, **58**: 1–30.

[145] Rivolta (1832–1893) was educated as a veterinarian and taught pathology and pathological anatomy, from 1868, as Professor at Pisa. He first observed fowl pox inclusions in 1869, but retired early due to illness.

[146] Otto von Bollinger, 'Über Epithelioma contagiosum beim Haushuhn und die sogenannten Pocken des Geflügels', *Virchows Arch. path. Anat. Physiol.*, 1873, **58**: 349–361.

[147] It was in experiments with fowl pox that the technique of culture of viruses on the chorio-allantoic membrane of the developing egg was first established; see A. M. Woodruff and E. W. Goodpasture, 'The susceptibility of the chorioallantoic membrane of chick embryos to infection with the fowl-pox virus', *Am. J. Path.*, 1931, **7**: 209–222.

Italian pathologist, Francesco Sanfelice,[148] who originally studied the lesions because of their similarity to cancerous tumours, and who in 1897 believed that he had identified the pathogen as belonging to the *Blastomycetes* group of fungi.[149] Later he realized his mistake and correctly placed the agent in the group of filterable viruses; moreover, he became an early exponent of the view that this type of pathogen could best be described as a chemical substance, and in 1914 Sanfelice published results which indicated that the substance might belong to the nucleoproteins.[150]

The question of the inter-relationship of vaccinia and variola which had so exercized the minds of the members of the French Academy of Medicine since Chauveau's first studies, was taken up in Britain by S. Monckton Copeman in the late nineteenth and early twentieth centuries, just as the new concept of filterable viruses was emerging. Copeman was familiar with Burdon-Sanderson's and Chauveau's papers of the 1860s,[151] but, unlike them, he reached the conclusion that the agents of smallpox and of vaccinia were essentially identical, and that vaccinia could be produced in the calf by inoculation of lymph from "... a mild and strictly localised form of small-pox ... induced in the monkey by inoculation of material from cases of the generalised disease in man ...". His results left him convinced that "... the vaccinia of Jenner's time was derived, in all probability, from a comparatively mild form of human small-pox".[152] As late as 1937, T. J. Mackie and C. E. van Rooyen seemed to make no distinction between the two when, discussing the relative contributions made by Buist and by Paschen, they wrote suggesting the name *Buistia pascheni* "as the specific name of the variola-vaccinia virus".[153]

Monckton Copeman's study of the inter-relationship of the viruses of vaccinia and variola was published in 1903. Five years earlier, in the Milroy Lectures for 1898, he had discussed at length his own extensive research into the nature of the agent of vaccinia, including perhaps the first known attempt to grow a virus in the hen's egg, not only before the pox viruses had been formally included in the group of filterable viruses, but in fact just as the group as such was becoming established. Copeman described in detail his reasons for choosing eggs for his purpose, and added the tantalizingly casual remark: "... the hen's egg, which has already been made use of as an alternative culture medium". Unfortunately he neglected to tell his readers where or how, or by whom, it had previously been used, and there is no literature reference;[154] and in any case he also added that he had "no experience to guide me as to the best method of carrying out the inoculation of the egg ...".[155] He seems

[148] Francesco Sanfelice (1866–1945) was born in Rome and educated at Naples. He held a number of chairs at different Italian universities before his final appointment at Pisa, from 1931.

[149] F. Sanfelice, 'Ueber die pathogene Wirkung der Blastomyceten', *Z. Hyg. InfektKrankh.*, 1897, **26**: 298–322.

[150] F. Sanfelice, 'Untersuchungen über das *Epithelioma contagiosum* der Tauben', ibid., 1914, **76**: 257–281.

[151] Copeman, op. cit., note 102 above, see p. 86; cf. also notes 125 and 128.

[152] S. Monckton Copeman, 'The inter-relationship of variola and vaccinia', *Proc. R. Soc. Lond.*, 1903, **71**: 121-133, see p. 133.

[153] T. J. Mackie and C. E. van Rooyen, 'John Brown Buist (1846–1915): an acknowledgement of his early contributions to the bacteriology of variola and vaccinia', *Edinb. med. J.*, 1937, **44**: 72–77, see p. 77.

[154] Copeman, op. cit., note 102 above, see p. 109.

[155] Ibid.

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to have achieved some degree of proliferation of the virus in eggs, when they were kept on beds of cotton-wool in an incubator at a temperature of 37 °C; but his experiments were not extensive, and the results not very clear. The book as well as the papers repeatedly draw attention to what remains Copeman's main contribution in this area, namely the introduction of "glycerinated lymph".[156]

By now, just before the turn of the century, work on the viruses of the mosaic disease of the tobacco plant and of foot-and-mouth disease in cattle had established the existence of what was henceforth to be known as "filterable" or "invisible" viruses. The large size of the pox viruses,[157] and the difficulty in purifying them, made them no easy object for filtration in the early years; the first to be included, on account of invisibility rather than filterability, was the virus of rabbit myxomatosis, by Sanarelli, in 1898.[158] Failing to find any activity in filtered lymph, Sanarelli obtained, by use of centrifugation, an "optically completely pure and totally sterile serum"[159] which retained full infectivity. If Sanarelli was unable to distinguish any particles in the "completely pure and totally sterile serum", others were soon to make observations to match Buist's "spores of micrococci" and Keber's "nuclei and molecules" in what were now more sophisticated studies.

In 1901, Calmette and Guérin, perhaps better known for their work on tuberculosis,[160] studied the considerable advantages in using the rabbit as experimental animal to test the strength of different batches of vaccinia lymph of different age and origin.[161] In the course of this study they observed in the vaccinia lymph used numerous minute refractive particles which they suspected of being the transmissible agent.[162] Guérin continued the study and by 1905 had developed a quantitative method for the evaluation of what he called "Jennerian vaccines", based on a simple count of active particles on shaved, inoculated rabbit skin.[163]

Also in 1905, von Prowazek turned his practised microscopist's eye to vaccinia lymph,[164] confirming the observations of Calmette and Guérin, and pointing out that Chauveau, nearly forty years earlier, had labelled such particles *granulations* .

[156] The addition of glycerol to vaccinia lymph (and to bacteriological samples in general) had been practised before by others, but Copeman firmly established the principle.

[157] The viruses of vaccinia and variola measure approximately 250–300 x 200 nm; by way of comparison, corresponding average values are: for influenza viruses, 80–120 (diam); for foot-and-mouth disease virus (isometric), diam. 20–25; for tobacco mosaic virus 300 x 18; and for *Escherichia coli*, 1000–2000.

[158] G. Sanarelli, 'Das myxomatogene Virus. Beitrag zum Studium der Krankheitserreger ausserhalb des Sichtbaren', *Zentb. Bakt. ParasitKde*, 1898, Abt. I, **23**: 865–873.

[159] Ibid., p. 869.

[160] Albert Calmette (1863–1933) was chosen to direct the Institut Pasteur in Lille when it was established in 1894, where he was joined by Camille Guérin (1872–1961). Guérin was later to write: "No-one will be able to reproach me for having touched on too many subjects without devoting the necessary time to each: I have studied only two problems, Jennerian vaccination and tuberculosis." Their important work on BCG vaccines long remained controversial, and only Guérin survived to see it fully vindicated.

[161] A. Calmette and C. Guérin, 'Recherches sur la vaccine expérimentale', *Annls Inst. Pasteur, Paris*, 1901, **15**: 161–168.

[162] Ibid., p. 166: "... une multitude de grains extrêmement petits, réfringents, mobiles, qui semblent bien être les éléments virulents du vaccin . . .".

[163] C. Guérin, 'Contrôle de la valeur des vaccins Jenneriens par la numération des éléments virulents', *Annls Inst. Pasteur, Paris*, 1905, **19**: 317–320.

[164] Von Prowazek, op. cit., note 126 above.

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élémentaires. Von Prowazek adopted the term, translating it into German, and appended illustrations (Figure 2) clearly showing elementary bodies, stained after Giemsa. The following year Paschen[165] modified Loeffler's flagellar stain for preparations of vaccinia and variola lymph, and identified himself with the belief that the elementary bodies observed were the infective particles. In recognition of Paschen's extensive studies in this field the bodies subsequently have been referred to as "Paschen bodies".

The year 1905 saw another important development in the study of the virus of vaccinia. Negri, who two years earlier had recorded his observations of the inclusion bodies in rabies material which have since borne his name,[166] succeeded in passing the virus from material freshly collected from a heifer, and diluted with ten to twelve times its weight of distilled water, through a Berkefeld V filter.[167] Soaking a pad of cotton-wool in the filtrate, Negri placed this in contact with a scratch on the cornea of a rabbit. After a period of about sixty hours, microscopic examination revealed the presence of typical Guarnieri bodies in the corneal cells.[168] With the corneal material Negri was subsequently able to reproduce characteristic vaccinia pustules on the cow's udder.

Von Prowazek's main interest in vaccinia was not really in the elementary bodies, but in the larger inclusions first observed by Guarnieri.[169] They became a cornerstone in his theory of *chlamydozoa*, or "mantled animals", the term invented by von Prowazek to designate the inclusion bodies characteristic of rabies, pox virus diseases, fowl pest, *molluscum contagiosum*, and trachoma, all of which furnished material for his keen histological studies.[170] Although von Prowazek was primarily a protozoologist and coined the name *chlamydozoa* for the viral inclusion bodies, he seems never seriously to have considered them to be protozoa; because of their differential reaction to the Giemsa stain he assumed from the beginning that the "mantle" was a product of the host cell formed in response to the invasion by elementary bodies.[171] Consequently he had no difficulty in accepting Lipschütz' modification of his theory, presented two years later, in 1909, which used the term "strongyloplasma" for the same group of agents, emphasizing the role of the granules, or elementary bodies, as the actual pathogen.[172]

Lipschütz and von Prowazek also brought their considerable talent in the field of microscopy to bear on another, far less intensively studied, pox virus disease, that of *molluscum contagiosum*. If this pox virus disease has received far less attention than

[165] E. Paschen, 'Was wissen wir über den Vakzineerreger?', *Münch. med. Wschr.*, 1906, **53** (ii): 2391–2393.

[166] A. Negri, 'Beitrag zum Studium der Aetiologie der Tollwuth', *Z. Hyg. InfektKrankh.*, 1903, **43**: 507–528.

[167] A. Negri, 'Sulla filtrazione de virus vaccinico', *Lo Sperimentale*, 1905, **59**: 679–680.

[168] A. Negri, 'Ueber Filtration des Vaccinevirus', *Z. Hyg. InfektKrankh.*, 1906, **54**: 327–346, see pp. 332–333.

[169] Guarnieri, op. cit., note 140 above.

[170] See S. von Prowazek, 'Chlamydozoa', *Arch. Protistenk.*, 1907, **10**: 336–358.

[171] Staining revealed two distinct components of the bodies, i.e., tiny reddish granules embedded in an amorphous blue substance; ibid.

[172] B. Lipschütz, 'Ueber mikroskopisch sichtbare, filtrierbare Virusarten (Strongyloplasmen)', *Zentbl. Bakt. ParasitKde*, 1909, Abt. I, Orig., **48**: 77–90.

most others, its inclusion bodies do have the distinction of having been observed and recorded long before those of variola and vaccinia, and even of fowl pox.[173] As early as 1841, two papers in the *Edinburgh Medical and Surgical Journal* described the inclusions, and one of the papers, by Robert Paterson, included meticulously drawn illustrations of their structure.[174] Von Prowazek did not long survive the outbreak of World War I;[175] but Lipschütz' main contribution was to come, years later, in the field of the herpes viruses.[176]

While in the first decade of the twentieth century the attention of many pathologists was focused on the inclusion bodies characteristic of rabies and of pox virus diseases, and on the elementary bodies visible in vaccinia lymph, zoologists and embryologists had a new dimension made available to them by use of Harrison's "hanging drop" method. Ross G. Harrison had devised this technique by 1907 in order to study the development of living nerve cells;[177] continually modified and improved over the next thirty years and more, it became the tissue culture method we know today as a most important tool for the study of viruses *in vitro*.

Since the inability of the filterable viruses to grow in or on conventional culture media was recognized as a stumbling-block almost from the outset, Harrison's method was soon tried out in virus research. In 1913, an attempt was made at the College of Physicians and Surgeons in New York City to grow vaccinia virus by means of the new technique.[178] It was found to multiply in cultures prepared with rabbit cornea, already a favourite object for the development of Guarnieri bodies and Paschen bodies, but not in cultures made with tissue from mammae, heart or liver of rabbits and guinea pigs. Soon afterwards, Noguchi claimed a measure of success with a similar method, using testicles of rabbits and bulls as the preferred tissue.[179] Ten years later, Parker and Nye also used tissue of rabbit testis, and obtained an impressive degree of proliferation of vaccinia virus in cultures which were maintained for periods of several months.[180]

Such results augured well for planned production of specific viruses. Alexis Carrel had initially interested himself in tissue culture as a prospective method for long-term maintenance of whole living organs.[181] At about this time he developed the flask

[173] Cf. notes 145 and 146 above.

[174] Robert Paterson, 'Cases and observations on the *molluscum contagiosum* of Bateman, with an account of the minute structure of the tumours', *Edinb. med. surg. J.*, 1841, **56**: 279–288.

[175] Stanislaus von Prowazek, born in Bohemia in 1875, died in a prisoner-of-war camp in Cottbus, north east of Dresden, early in 1915, a victim of the typhus fever he was there to study, as representative of the Ministry of War.

[176] B. Lipschütz, 'Untersuchungen über die Ätiologie der Krankheiten der Herpesgruppe, (Herpes zoster, Herpes genitalis, Herpes febrilis)', *Arch. Derm. Syph.*, 1921, **136**: 428–482.

[177] R. G. Harrison, 'Observations on the living developing nerve fiber', *Proc. Soc. Exp. Biol. Med.*, 1907, **4**: 140–143.

[178] Edna Steinhardt, C. Israeli and R. A. Lambert, 'Studies on the cultivation of the virus of vaccinia', *J. infect. Dis.*, 1913, **13**: 294–300; Edna Steinhardt and Robert A. Lambert, 'Studies on the cultivation of the virus of vaccinia II', ibid., 1914, **14**: 87–92; see also Edna S. Harde, 'A propos de la culture du vaccin', *C.r. Séanc. Soc. Biol.*, 1915, **78**: 545–546.

[179] H. Noguchi, 'Pure cultivation *in vivo* of vaccine virus free from bacteria', *J. exp. Med.*, 1915, **21**: 539–570.

[180] F. Parker and R. N. Nye, 'Studies on filterable viruses. I. Cultivation of vaccine virus', *Am. J. Path.*, 1925, **1**: 325–335.

[181] Alexis Carrel (1873–1944), in the course of a colourful and sometimes controversial career,

culture method for use with larger quantities of tissue;[182] and soon afterwards he was able to devise a technique for routine production of Rous sarcoma virus.[183] The following year, 1927, Carrel and Rivers found that a similar procedure was suitable for the production of substantial quantities of vaccinia lymph.[184] Carrel concluded that, "It is probable that a chick embryo crushed to a fine pulp is capable of producing as much vaccine as a calf", adding that their technique should be suitable for adaptation to large-scale industrial production of pure vaccinia virus.[185] Carrel in 1928 was also well aware both of the future possibilities of tissue culture for virus research, and of the difficulties which must be faced. He wrote: "Certain viruses probably have the property of growing without modifying the cells which they use as a substratum, as happened with macrophages in the presence of Rous virus. Other viruses will, without doubt, produce characteristic lesions, such as have been observed in the tissues of living animals. It is possible that, according to the living or non-living nature of the virus, the cytological changes in the cells will assume profoundly different characteristics. At the same time, it will be easy to observe how the reactivity of a given strain of cells is modified by a virus . . .".[186]

In the same year, 1928, the Maitlands in Manchester obtained proliferation of vaccinia virus of the order of 25 x 10^6 through four successive cultures of the virus in a medium of finely minced hen's kidney diluted with Tyrode's solution[187] and hen's serum, subsequently to be known as "Maitland's medium" or the "Maitland and Maitland tissue system". Years later this medium was modified to be used for large-scale production of polio virus for Salk vaccine. The Maitlands could detect no tissue growth in the course of their experiments; on the contrary, the kidney fragments were beginning to disintegrate after twenty-four hours, and eventually autolysis was complete. Hence they initially described their method as "cultivation of vaccinia virus without tissue culture".

Tissue culture was not the only one of the techniques intimately associated with virus research which was markedly improved in the 1920s. Ultrafiltration, pioneered by Bechhold[188] and with important modifications by Elford,[189] and ultracentrifugation with the instruments first designed by Svedberg and Fåhraeus[190] yielded data

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was awarded the Nobel Prize in 1912 for work on vascular suture and transplantation of blood vessels and organs, and eventually, amid a blaze of publicity, developed the artificial heart in collaboration with Charles Lindbergh.

[182] A. Carrel, 'A method for the physiological study of tissues *in vitro*', *J. exp. Med.*, 1923, **38**: 407–418.

[183] A. Carrel, 'Some conditions of the reproduction *in vitro* of the Rous virus', ibid., 1926, **43**: 647–668.

[184] A. Carrel and T. M. Rivers, 'La fabrication du vaccin *in vitro*', *C.r. Séanc. Soc. Biol.*, 1927, **96**: 848–850.

[185] A. Carrel, 'Tissue cultures in the study of viruses', in T. M. Rivers (editor), *Filterable viruses*, Baltimore, Md., Williams & Wilkins, 1928, see p. 105.

[186] Ibid., p. 107.

[187] H. B. Maitland and M. C. Maitland, 'Cultivation of vaccinia virus without tissue culture', *Lancet*, 1928, **ii**: 596–597.

[188] H. Bechhold, 'Kolloidstudien mit der Filtrationsmethode', *Z. phys. Chem.*, 1907, **60**: 257–318.

[189] W. J. Elford, 'The principles of ultrafiltration as applied in biological studies', *Proc. R. Soc. Lond., B*, 1933, **112**: 384–406.

[190] The Svedberg and R. Fåhraeus, 'New method for the determination of the molecular weight of the proteins', *J. Am. Chem. Soc.*, 1926, **48**: 430–438.

which suggested that the size of the virus of vaccinia and of other pox viruses placed them at the very top of the table of virus sizes.[191] Even before the advent of the ultracentrifuge, centrifugation at what was then referred to as "high speed" had been used in the method of differential centrifugation, devised as a means of concentrating virus suspensions with the virus of vaccinia as experimental model, by MacCallum and Oppenheimer in 1922.[192]

Elford had been introduced to ultrafiltration when he first joined J. E. Barnard, who was a friend of Bechhold.[193] Throughout the 1920s, Barnard improved his microscopical techniques, introducing ultraviolet microphotography into virus research and tirelessly attempting to make increasing numbers of the elusive filterable viruses visible in his microscopes.[194] A born microscopist, his measure of success was nevertheless limited by the means at his disposal; further real progress was to be made only after electron microscopes became generally available for this type of work, at the end of World War II.[195]

In 1948, two studies appeared, one in the United States and one in Canada, which demonstrated the usefulness of the electron microscope in smallpox diagnosis. For the first time photographs were shown of the viruses of vaccinia, variola, and varicella as they now appeared at the greater magnification made possible.[196] The illustrations complemented photographs published the previous year of lesions on the chorio-allantois of the chick embryo infected with the viruses of vaccinia and variola.[197] The technique used for the latter study had first been developed for work on a related animal virus, that of fowl pox, in 1931;[198] it has become a method of the utmost importance for work not only on all the pox viruses, but on a number of other viruses as well, including the influenza viruses of man, beast, and bird. In the decade following the end of World War II, the introduction of metal shadowing[199] and staining of samples with phosphotungstic acid[200] brought great improvements to the images of pox viruses obtained, and eventually some of the finer structure became discernible.[201]

[191] See W. J. Elford, 'The sizes of viruses and bacteriophages, and methods for their determination', in R. Doerr and C. Hallauer (editors), *Handbuch der Virusforschung*, vol. I, Vienna, Julius Springer, 1938.

[192] W. G. MacCallum and E. H. Oppenheimer, 'A method for the study of filterable viruses, as applied to vaccinia', *J. Am. Med. Ass.*, 1922, **78**: 410–411.

[193] See 'William Joseph Elford (1900–1952)', in *Obit. Not. Fell. R. Soc. Lond.*, 1952–53, **8**: 149–158.

[194] See Elford, op. cit., note 191 above, pp. 181–191.

[195] See 'Joseph Edwin Barnard (1870–1949)' in *Obit. Not. Fell. R. Soc. Lond.*, 1950–51, **7**: 3–8.

[196] C. E. van Rooyen and G. D. Scott, 'Smallpox diagnosis with special reference to electron microscopy', *Canad. J. publ. hlth*, 1948, **39**: 467–477; and F. P. O. Nagler and G. Rake, 'The use of the electron microscope in diagnosis of variola, vaccinia and varicella', *J. Bact.*, 1948, **55**: 45–51.

[197] A. W. Downie and K. R. Dumbell, 'The isolation and cultivation of variola virus on the chorio-allantois of chick embryos', *J. Path. Bact.*, 1947, **59**: 189–198.

[198] See note 147 above.

[199] Introduced by R. C. Williams and R. W. G. Wyckoff ('Electron shadow micrography of virus particles', *Proc. Soc. Exp. Biol. Med.*, 1945, **58**: 265–270) who used samples of PR-8 influenza virus and of tobacco mosaic virus. The technique was soon employed on the virus of vaccinia as well, see D. G. Sharp, A. R. Taylor, A. E. Hook and J. W. Beard, 'Rabbit papilloma and vaccinia viruses and T_2 bacteriophage of *E. coli* in "shadow" electron micrographs', ibid., 1946, **61**: 259–265.

[200] C. E. Hall, 'Electron densitometry of stained virus particles', *J. Biophys. Biochem. Cyt.*, 1955, **1**: 1–12.

[201] See, for example, J. N. C. Westwood, W. J. Harris, H. T. Zwartouw, D. H. J. Titmuss, and G. Appleyard, 'Studies on the structure of vaccinia virus', *J. gen. Microbiol.*, 1964, **34**: 67–78.

Just before the outbreak of war in 1939, a research group at the Rockefeller Institute had succeeded in purifying vaccinia virus sufficiently to carry out chemical studies on their material. Their subsequent work established that the purified virus contained substantial amounts of DNA and little, if any, RNA.[202] Two decades later, the understanding of viruses and the mechanisms involved in their *modus operandi* and infectivity had improved manifold, and more sophisticated studies of pox virus DNA were possible. Among the interesting results obtained was the demonstration of the ease with which genetic recombination takes place between different related pox viruses[203] and the overall close similarity of the DNA of different strains. Four pox virus strains (one vaccinia, one rabbit pox, one cowpox, and one ectromelia) were found to be indistinguishable with regard to their DNA content and its base composition by the methods employed.[204] At the same time, improved methods have been used to explore the behaviour of variola virus in tissue culture.[205]

Armed with such an accumulation of essential basic knowledge, and with so many sophisticated techniques, it would seem that we are reasonably well equipped to control any future outbreaks of known or unknown pox viruses. Perhaps one of the most spectacular of the new techniques which the molecular geneticists have developed in recent years and which allows them to determine the sequence of nucleotides in small viruses,[206] will eventually enable them also to present a definitive solution to the age-old question of the identity and inter-relationship of vaccinia and the other huge pox viruses.

SUMMARY

Because of its wide distribution, high infectivity, and high fatality rates in many outbreaks, smallpox has attracted much attention throughout the centuries. The resulting copious literature has consequently reflected general attitudes to infectious disease, and concepts such as infectivity, transmissibility, and immunity (acquired naturally or by inoculation and, later, vaccination) have probably had more early attention in relation to smallpox than to most other infectious diseases. In the present paper an attempt is made to follow the changing fortunes of the above concepts as reflected in selected studies of the disease from the tenth century to the present day.

[202] J. E. Smadel, G. I. Lavin and R. J. Dubos, 'Some constituents of elementary bodies of vaccinia virus', *J. exp. Med.*, 1940, **71**: 373–389; and C. L. Hoagland, G. I. Lavin, J. E. Smadel and T. M. Rivers, 'Constituents of elementary bodies of vaccinia. II. Properties of nucleic acid obtained from vaccinia virus', ibid., 1940, **72**: 139–147. This work is discussed in detail, as is the all too brief but remarkable career of Charles Lee Hoagland (1907-1946), in George W. Corner, *A history of the Rockefeller Institute 1901-1953*, New York, Rockefeller Institute Press, 1964, see pp. 464-465, and 477-480.

[203] See, for example, G. M. Woodroofe and Frank Fenner, 'Genetic studies with mammalian poxviruses. IV. Hybridization between several different poxviruses', *Virology*, 1960, **12**: 272–282.

[204] W. K. Joklik, 'The purification of four strains of poxvirus', ibid., 1962, **18**: 9–18.

[205] See, for example, M. Baltazard, A. Boué and H. Siadat, 'Etude du comportement du virus de la variole en cultures de tissus', *Annls Inst. Pasteur, Paris*, 1958, **94**: 560–570; and N. Hahon, 'Cytopathogenicity and propagation of variola virus in tissue culture', *J. Immunol.*, 1958, **81**: 426–432.

[206] A sequence for the small coliphage Phi X 174 was determined in 1977; see F. Sanger, G. M. Air, B. G. Barrell, N. L. Brown, A. R. Coulson, J. C. Fiddes, C. A. Hutchinson III, P. M. Slocombe and M. Smith, 'Nucleotide sequence of bacteriophage Phi X 174 DNA', *Nature, Lond.*, 1977, **265**: 687–695. This tiny phage is of the same order of magnitude as foot-and-mouth disease virus, cf. note 157 above.