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An Introduction to the HISTORY OF VIROLOGY

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'Many shall run to and fro, and knowledge shall be increased.'

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A selection of tulip flowers showing various distinctive patterns characteristic of infection with tulip mosaic virus. The original colour plate, painted by Philip Reinagle, R.A., is included in *The Temple of Flora* (London, 1799), by John Robert Thornton, a graduate of Trinity College, Cambridge, and Guy's Hospital Medical School, who became a lecturer on medical botany at the United Hospitals of Guy and St Thomas'. Thornton's consuming interest in botanical engaving led him into over-ambitious publishing ventures (including *The Temple of Flora*), and his later life, until his death in 1837, was beset with financial difficulties.

'Of the three adjectives which might be employed to express the idea that contagium consists of particles, viz. molecular, corpuscular and particulate, the former, although more familiar, are objectionable, because the words from which they are derived have already been appropriated. "Molecule" is understood in physics to mean a hypothetical body of indefinite minuteness, while "corpuscle" is used in anatomy to denote bodies of much larger size than those in question.'

Burdon Sanderson, 1869

'In order to determine whether the virus [tobacco mosaic virus] should be considered as corpuscular or as dissolved the following experiment was devised... Hence there appears to be little doubt that the contagium must be regarded as liquid, or perhaps better expressed, as water-soluble.'

M. W. Beijerinck, 1898

'...this suggestion also had its repercussions, for whether or not viruses were particulate was solemnly debated, without anyone apparently asking what they could be if they were not particles of some size or other.'

F. C. Bawden, 1964

Aims, possibilities and objectives

by A. P. Waterson

The word virology itself is very recent, and the science of virology not much older, so that some may question even whether it has much of a history to write. In fact, as a study in the history of science it has proved rewarding. Its relatively recent origin means that the sources are copious and, on the whole, accessible, even if they are somewhat diffusely spread. Many of the people involved in some of the quite early work are still alive. Very much has happened in a short time, so that the rate and acceleration of growth of knowledge have been so fast that the direction and flow of thought have been easy to follow. The origins are various, but easy to discern. Botany, plant pathology, human and veterinary medicine, and especially that activity known as hygiene on the continent of Europe and as bacteriology in Great Britain and the United States, whether by doctors or veterinarians, have all contributed. As time went on, and momentum was gathering, genetics, protein chemistry, cytology and molecular biology all became involved.

It was in fact a consideration of virology as an offshoot of bacteriology, and an experience of the difficulties of working in a young subject under the terms of reference of an old, which supplied much of the stimulus to initiate the current study. Indeed, the development of virology could, with profit, be studied by historians as a model of the emergence and establishment of a new branch of biological science. The shifts of academic and organizational thrust, the ebb and flow of emphasis, and the forces behind them, comprise in themselves a valuable model system. The rise and fall of research institutes, the inception of new academic courses, the effects of rigidly determined medical curricula, the interplay between pure and

applied science, have all played a part in the genesis of virology. Not least, the subject could serve as a *locus classicus* for anyone wishing to study the relation between scientific research and medical practice, using the term in its widest sense. Such a study would necessarily involve a consideration of the cross-linkages between disciplines and groups of disciplines, especially between the physical and chemical, on the one hand, and the biological, on the other. For example, the Max Planck Institute for Virus Research at Tübingen sprang not from a microbiology laboratory but from an institute for research in biochemistry.

Surprisingly, one of the most potent, if somewhat subterranean, influences has been that of the atomic physicists of the 1920s, principally Erwin Schrödinger, whose book *What is life?* proved seminal to modern molecular biology and to viral genetics. Ostensibly it was because they hoped to find 'new laws' that such investigators as Schrödinger and Delbrück were interested in biological phenomena. The preoccupation of physicists at this time with sub-atomic particles may also have given them a fellow feeling with microbiologists dealing with what seemed, on their scale, to be infinitely, and indeed impossibly, small particles.

This very element of near impossibility with which the early virologists were faced makes the subject a fertile one for the historian on two accounts. The principal difficulties were those intrinsic to the study of very small biological particles, and the pioneers had little at hand in their armamentarium. However, sooner or later, techniques did emerge. Centrifuges grew in speed and power, and microscopes were developed until their resolution and magnification went beyond what the specimen and the preparative techniques merited. In the meantime, the methods available were stretched to their limits, and it would be a rewarding study to find out how far the problem stimulated the technical development, and vice versa. Certainly in one field, that of cell and tissue culture, the demands of virology supplied a powerful *vis a tergo* to the technique, which at one time was in danger of becoming an inward-looking mystique.

The second reason why the early experimental inaccessibility of the small particles is of interest is that it is now possible, by hindsight, to judge how correct, or otherwise, were the ideas

and the concepts formed by the early virologists about the agents they studied. In other words, their mental concepts of what they were studying can be examined, and the development of these concepts studied, together with the influences which played upon them, and the reasons for which they elaborated the pictures they did of what they could not see. The evaluation of size from indirect evidence and the beneficial effect of an increasingly quantitative approach plays an interesting part in the development of thought in this area. What is of particular interest is how early this began to happen. Beijerinck was thinking in molecular terms before the turn of the century, but was not matched by the organic chemists of his day. Ideas on the size of large molecules came to the fore surprisingly early, but the birth pangs of the macromolecular concept make surprising reading today in an age of polymer chemistry, and are an object lesson in the difficulty of accepting a scientific concept when it does not fit in with what has been accepted, entrenched and even cherished.

In the light of all this, it is clear that several different histories of virology might have been written. Of course, each would embrace the same general series of events but each would concentrate on one or other facet of the whole story. For example, it could have taken the form of an account of the various academic and other environments in which virology grew up. This would be of great interest to anyone interested in the founding of new subjects and the organizational obstacles which have to be overcome when this happens. It would be a study of how a subject becomes a subject, and what justification it may have for enjoying all that this entails in terms of accommodation, research funds and, within a university, teaching facilities. Again, the history might have concentrated on the experimental basis alone, i.e. on the discoveries made, the technical problems involved and the technical solutions to them, including the influence of such techniques on fields outside virology. Another approach would have been the biographical one. It would have concerned itself with the personalities involved, with what made them incline to this particular field, what made them excel in it, and, when they failed and were held up, why this should have happened. Of course, all these three

elements are essential as ingredients, but the proportions used, and their quantities relevant to each other, would vary from one account to another.

In fact, the approach chosen has been different from all of these, although in varying degrees it has embraced each of them. The underlying theme of this book, which is to be viewed as an *aditus* to the subject as a whole, is the evolution of the present concept of a virus. This present-day concept is essentially a chemical one, but that is not to imply that it is divorced from the mainstream of *biological* thinking, but, because it is chemical, and because definition cannot proceed further than molecules, it is to be regarded as definitive, and the present time as a good vantage point from which to look back, so that we can better look around and better look forward. It is therefore essentially apocalyptic, in the proper sense of the word, i.e. revelatory. It is possible to study the virological scientists of the past, and to know in the light of present knowledge exactly what they were studying, even though this was not revealed to them in their day. It is, in other words, the story of the progressive unveiling of the nature of the virus particle.

This history is therefore essentially, and indeed deliberately, *conceptual.* It is a study of ideas and concepts, and the interreactions between these, on the one hand, and experiment and technique, on the other. That it is inextricably interwoven with the administrative, the technical and the personal goes without saying, and to compose this history involved in itself the administrative, the technical and the personal. It involved the administrative, because it was initiated in the belief that the work could best be done in an orthodox academic department of virology, but by a full-time and committed historian, and this is how it came into being. It involved the technical, because it was necessary to devise a historical technique by which the necessary examination, analysis and synthesis could be achieved. It is apposite here to outline this method. Four well-studied viruses were chosen. These were fowl plague (avian influenza A), tobacco mosaic, rabies and smallpox.[1] All were early on the scene, all have been exhaustively studied. Their history was

[1] These and an introductory paper have been published in *Medical History.*

studied with particular attention to the ideas in the minds of the succession of scientists concerned about the nature, or essence, of the agent with which they were dealing. What was it in terms of known biological phenomena? What was its chemical constitution? How big was it? Above all, was it something *sui generis*, or was it another example of something already known? This provided four bodies of information, each in chronological sequence, so that the conceptual activities of virologists on at least four agents could be compared at any one point in time, especially in the last 90 years. This provided a frame of reference of fixed points in time and thought, against which other material could be assessed. This was then collated with the general discourses and reviews on the whole field which have appeared from time to time, and such 'battles long ago' as the now burnt-out controversy as to whether viruses are 'living' or 'non-living', seen in perspective. The resulting synthesis constitutes the main corpus of this book.

The third element has been the personal. A catalogue may be compiled by a computer, but stories can be told only by a person. Inevitably, as persons too, individual virologists figure in these pages, but it is their thinking as much as their doing with which we have been concerned, because the lesser (doing) is included in the greater (thinking). Biographical details have been relegated to an appendix, not because they are unimportant, but to prevent them from obstructing the main flow of the narrative. Narrative is perhaps a key word, because this is, above all, a story. It is to be hoped that, as a story, it will be read with enjoyment no less than, as a history, it will be studied with interest.

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Inclusion of the colour frontispiece was made possible by a grant from the Wellcome Trust which is gratefully acknowledged. The plate was reproduced from the original volume of *The Temple of Flora* in the Library of Eton College, by courtesy of its Provost and Fellows.

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1. Early terminology and underlying ideas

The term *virology* has become part of our vocabulary only gradually during recent decades. The first edition of S. E. Luria's *General Virology* was published in 1953, and the first issue of the journal *Virology* appeared in 1955. Viruses, on the other hand, have been with man for a very long time, and so has the word *virus*, although its connotations and usage have varied over the centuries.

Even the most liberal interpretation of accuracy of definition would allow us to date the history of any true concept of viruses only from the end of the nineteenth century. If we include epidemiological aspects in our historical considerations, we are still on uncertain ground with most virus diseases for the better part of our calendar, with one outstanding exception. Rabies, whose ravages in terms of human lives lost or affected are slight compared with the major scourges of mankind, has been meticulously described and recorded for more than two millennia. Its mysterious aetiology, its ability to transform a friendly, domesticated dog into a raging, vicious beast, its long and ill-defined incubation period, and the all too well-defined and infinitely distressing symptoms preceding the inevitable fatality of the frank clinical disease in man – all combined to present a picture which by its very terror made it irresistible to the writers and thinkers of antiquity. Comparisons of early Roman and Greek descriptions with recent case reports suggest that rabies virus has changed little if at all during the intervening years. This distinguishes it from most other pathogenic viruses known today, and gives it a unique position in history. Thoughts on the aetiology of rabies have been proffered to the world for a very long time, and the disease itself can be traced back at least

as far as Aristotle,[1] who informed his readers that '...rabies drives the animal mad, and any animal whatever, excepting man, will take the disease if bitten by a mad dog so afflicted; the disease is fatal to the dog itself and to any animal it may bite, man excepted' (17). Later commentators, many of whom were reluctant to question the credibility of the great philosopher, have been puzzled by the apparent reference to the insusceptibility of man, and have offered varying explanations,

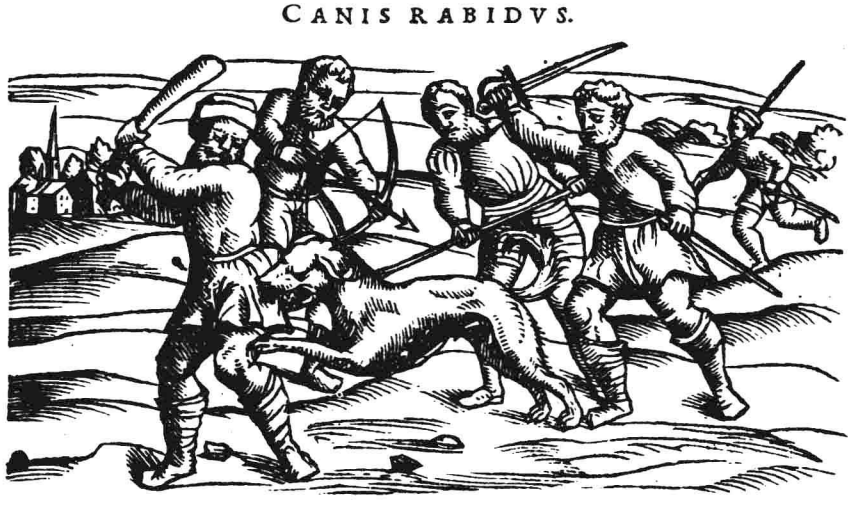

Fig. 1. Sixteenth-century woodcut showing men attempting to overpower a rabid dog. From Dioscorides (1566), *Acerca de la materia medicinal*, Salamanca: M. Gast. (Courtesy of the Trustees of the Wellcome Foundation.)

ranging from an early change in the syndrome to the more likely one, by Fracastoro (159) that Aristotle merely meant to draw attention to the fact that not all those bitten by a mad dog would necessarily develop the clinical disease.

A more detailed and remarkably accurate description of the

[1] Some other claims would appear to be less well founded. That Democritus 'considered the disease an inflammation of the nerves' is probably explained by an over-optimistic translation of Caelius Aurelianus' Latin rendering of Soranus' Greek texts (19). Democritus' contemporary, Euripides, is said to have been subjected to salt-water therapy by being thrown into the sea following a dog bite. This type of treatment was long adhered to – *faute de mieux* – and Boissier de Sauvages attempted to explain it in chemical terms in the eighteenth century (see 443; 444).

rabies syndrome was provided by Celsus, who lived and wrote during the heyday of the Roman Empire in the first century A.D. One particular sentence from Celsus' chapter on rabies has been extensively quoted. 'Especially if the dog was rabid, the virus must be drawn out with a cupping glass' (73). Of course no one would suggest that Celsus with these words identified the pathogen of rabies as a virus in modern terms; nevertheless, the apparent distinction he draws between the use of 'virus' to denote the agent of rabies and, later in the text, of 'venenum' to describe the poisonous principle from snakes may have been not wholly accidental. It may reflect the alternative meaning of 'slimy liquid' for 'virus' in Latin, and hence Celsus' awareness that the agent of rabies was transmitted through the (slimy) saliva of the rabid dog.

For centuries after Celsus, the term 'virus' was used casually as a synonym for poison or venom, until with the growing awareness of transmission of disease in the eighteenth and nineteenth centuries it eventually acquired the meaning of an infectious agent. The gradual acceptance of this usage in medical literature ran parallel to the development of the twin concepts of infection and contagion, and both owed much to another virus disease of exceptional historical interest. Unlike rabies, smallpox through the centuries has had a marked influence on the course of social and political history.

In terms of devastation frequently wreaked in mediaeval communities, smallpox is equalled among the infectious diseases only by bubonic plague, and this is one of the obvious reasons why smallpox played a major role for the popular acceptance of the principle of disease transmissibility. At the same time, the early history of smallpox presents a far greater problem to the historian than does rabies; the difficulties inherent in any attempt to establish differential diagnosis of smallpox and other eruptive fevers, such as measles, chickenpox, German measles, and even scarlet fever, on the basis of often vague and incomplete descriptions made several hundred years ago in Arabic or classical or mediaeval Latin, are daunting and frequently insurmountable. Even Fracastoro, whose perceptive sixteenth-century comments on contagion command the respect of anyone interested in the early development of this concept, had

A
DECLARATION
OF SVCH GREIVOVS
accidents as commonly follow
the biting of mad Dogges,
together with the cure
thereof,

BY
THOMAS SPACKMAN
Doctor *of* Phyſick.

LONDON
Printed for *Iohn Bill* 1613.

Fig. 2. Self-explanatory title page of Thomas Spackman's (1613) treatise on rabies, London. (Courtesy of the Royal Society of Medicine.)

little to contribute in his chapter on smallpox and measles. Although he fitted what he called collectively 'poxes and measles' (variolae and morbilli)[1] into his general theory of contagion with the remark '. . . what exhales from the putrefaction . . . is a germ of contagion for another individual. . .' (159) he was at pains also to associate himself with the idea inherited from the Arabic writers, notably Rhazes, that the eruptive fevers were a salutary and necessary form of purgation suffered to greatest advantage in childhood, the earlier the better.

But the lessons of the major smallpox epidemics of the seventeenth and eighteenth centuries, when particularly virulent strains struck the European continent, were obvious. Something was transmitted from person to person, from house to house. The practice of variolation may have had its origins in pagan, superstitious attempts to transfer evil afflictions to a third party. It was introduced into Europe in its established form from the Middle East, and, from 1721 onwards, was made fashionable in England and on the European continent when it was championed by Lady Mary Wortley Montagu[2] after her return from her husband's Constantinople Embassy. As a lesser evil, variolation enjoyed considerable popularity in informed circles until Jenner presented his safer alternative of vaccination in 1798.

The problems of the severe epidemics and the controversy surrounding the variolation procedures formed the basis for much medical literature in the late seventeenth and throughout the eighteenth century. In the course of their considerations, some authors allowed themselves space to speculate on the nature of the contagion; during the eighteenth century there was a growing tendency to label the principle transmitted 'virus'. Thomas Fuller, in 1730, included quite advanced views in his account of eruptive fevers, and wrote: 'The chief and commonest Way of taking the contagious Fevers, Small-Pox and Measles, is by Infection; that is, by receiving with the Breath,

[1] Fracastoro's chapter on poxes and measles is not among the most lucid in *De contagione et contagionis morbis et eorum curatione*, and his distinction between variolae and morbilli is vague (159).

[2] An interesting biographical sketch of Lady Mary has been supplied by Robert Halsband who has unearthed a letter suggesting that Timonis, who with Pylarino first introduced variolation in Europe and to the Royal Society (448; 361), was physician to the Embassy household at the time Lady Mary conceived the idea of variolation for her own children (196).