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Neutralizing Flu: 'Immunological devices' and the making of a virus disease

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In fall 1936, a team of virus researchers from the National Institute for Medical Research (NIMR) in London joined groups of physicians and pathologists at hospitals and military establishments in a crucial series of medical studies aimed at tackling the cause and control of influenza. Two years earlier, three NIMR workers, P.P. Laidlaw, Wilson Smith, and C.H. Andrewes, discovered that they could use ferrets to isolate a 'filterable virus' from flu patients and, with this research animal, begin to determine flu's identity as a 'virus disease'. The discovery, noted the institute's director, Sir Henry Dale, had drawn flu 'within the realm of experiment', for it made it possible to elucidate the relation between the virus and the disease, and to explore the nature of flu immunity.[1] Within a year, the team had added a laboratory mouse to their experimental system and the animal became the basis for a serological test that enabled them to identify and measure 'neutralizing' antibodies associated with the virus, and thus indirectly determine its presence in human populations. These developments went far towards transforming flu into an object of virus research. But establishing flu's viral identity required more than a working experimental system. As the NIMR workers knew, such efforts would hinge on their ability to link the virus disease they developed in ferrets and mice with what the medical profession and public health authorities knew as 'influenza'. The team had to confront the critical problem of how to make a laboratory object relevant to constituencies outside the laboratory walls. It was to this end that the NIMR, through its governing body, the Medical Research Council (MRC), initiated its collaborative research scheme to correlate laboratory and clinical knowledge in support of a new definition of flu.

Since the NIMR was a freestanding research institution with no formal connections to metropolitan or military hospitals, the team recruited a young physician from St. Bartholomew's hospital in London, C.H. Stuart-Harris, as their lead clinical researcher and charged him with developing clinical alliances and coordinating the clinical work. The NIMR workers hoped that by collaborating with clinicians and pathologists in London hospitals they could align the virus with a specific clinical entity, and thereby solve the long-standing medical question of what constituted 'influenza'. The construction of flu's virus identity would thus involve the simultaneous construction of new social relations around the disease.

A generation of physicians, epidemiologists and medical researchers knew flu as a remarkably protean entity, the dangers of which had been dramatically revealed during the 1918 'Great Pandemic'. While the medical profession had started to recognize flu as an infectious disease in the early 1890s, four decades of laboratory work had failed to determine its cause or put its diagnosis and control on firm laboratory footings. Until 1933, most British medical textbooks, and much of the medical profession, assumed that flu's specific cause was a bacillus identified in 1892 by the reputed Berlin bacteriologist, Richard Pfeiffer. Though claims supporting the role of a filterable virus surfaced during the 1918 pandemic, the issue of what caused flu remained undecided. The NIMR's investigative tools raised new hopes for a solution to this vexing problem. Stuart-Harris suggested that he and his colleagues were now in a position to delineate 'true influenza' from the 'scrap-heap' of conditions usually associated with the disease.[2] Besides the obvious diagnostic implications, linking the virus to a specific disease entity would also allow the team to test an experimental vaccine on known cases of flu virus infection. But while the prospect of developing new methods for the scientific management of the flu had already won the NIMR workers' research attention in the medical and lay press, their contribution to existing clinical and public health approaches was by no means self-evident. Establishing flu's viral identity meant legitimizing virus research as an investigative field. The NIMR's scheme was thus part of a complex process of positioning virus research – and virus workers – as indispensable to the elucidation and control of flu.

This re-positioning depended, to a large degree, on the ability of the NIMR researchers to move their work from the realm of experiment to the realm of medicine in hospitals and clinics. The production of tools for tackling medical problems associated with flu was an important way of bridging these realms. Yet not all the tools in the experimental set-ups of interwar virus research could serve this function. This paper concentrates on how a serological assay – the virus neutralization test – fashioned first through ferrets, and then through mice, gained characteristics of a boundary object that mediated the different social worlds through which flu was framed.[3] I trace the making of the NIMR's flu virus neutralization test and explore how, through its application to clinical and public health problems, it participated in the construction of both flu's viral identity and a group of virus workers necessary to the medical management of the disease. The multiple uses of these tests for the serological identification of flu virus, for tracking serum antibodies in Londoners, and for evaluating the efficacy of vaccines, enabled the NIMR workers to align their laboratory work with the interests and practices of medical constituencies who claimed ownership over the flu.

Neutralization tests, though widely used in the burgeoning field of interwar medical virus work, were also bound to the specific contexts in which they were deployed. As I show, the flu virus neutralization test reflected a particular research style developed at the NIMR. This style was defined by a particular orientation that construed viruses and virus diseases as problems best solved by the production and use of what NIMR workers called 'immunological devices'.[4] Historians, such as Ton van Helvoort, have suggested that this immunological orientation was largely the product of technical constraints and limitations of interwar virus work, which had its roots in bacteriology and serology.[5] While there is truth in this observation, interwar approaches to viruses and diseases need to be set in relation to broader professional and institutional concerns with the practical

applications of immunology to medicine.[6] Interwar virus workers used serological assays to demonstrate the ways in which the nascent field of virus research was applicable to the tangible problems of a disease's aetiology, epidemiology, and immunization. Demands for workable tools for clinical and public health medicine were thus an important factor in shaping the NIMR's immunological style of virus work. This research style was itself a manifestation of an ethos of scientific modernization promoted by the MRC that aimed to make the products of laboratory science relevant to medicine. Immunological devices were seen as particularly useful for realizing these goals.

Flu and the 'Filter-passers'

In early 1922, Walter Morley Fletcher, the pugnacious secretary of the new Medical Research Council, organized a meeting of leading British medical scientists and colleagues at the War Office to hammer out the details of a new scheme of research on the problem of 'filter-passing' viruses.[7] That the MRC had conceived this scheme in the wake of the First World War was no coincidence. Established in 1913, with limited responsibilities as a research committee for the National Health Insurance Commission, by war's end the MRC's authority had expanded over a wide range of medical problems and it had established methods of scientific and administrative organization that were judged relevant by government for the coordination of post-war medical research.[8] The MRC was rewarded for its wartime efforts by being granted status as a research council, which freed it from obligations to government departments and enabled it to pursue its own agendas.[9] Having used the war as an opportunity to define new areas of medical research as indispensable to military and civilian medicine, the MRC searched for new domains to bring under its remit. The still relatively unknown filter-passing viruses, which posed a host of problems for established laboratory technique, were seen as just the kind of complex object around which the MRC wanted to remake medical science.[10]

Yet there was a more immediate reason for the MRC's interest in the so-called 'filter-passers': the devastating 1918-19 flu pandemic. Comprising three epidemic waves that swept the globe between May 1918 and March 1919, the pandemic had killed an estimated 23,000 in London, 250,000 in Britain, and 50 million worldwide.[11] Nearly 65% of all those killed in Britain and the rest of the world died in a span of 8 to 10 weeks between October and December 1918.[12] The pandemic challenged the authority of the medical profession, as it eluded all known methods of treatment and prevention and, in industrial nations, revealed the limits of laboratory medicine.[13] But while many medical constituencies were indeed paralyzed by the pandemic, some, like the MRC, seized on it as opportunity. In particular, the MRC used research it supported during the pandemic to make connections between a filter-passer and flu, and to promote its new virus research scheme.

The MRC gained credibility during the pandemic from its collaboration with the War Office and Army Medical Services (AMS), and in coordinating laboratory investigations into the clinical pathology of flu.[14] At the time, British medical authorities shared the view that determining flu's cause was a key ingredient to its prevention.[15] They reckoned that once the primary agent was found, a flu vaccine, like those developed for typhoid, tetanus, or diphtheria, could be developed for effective use in military and civilian

populations.[16] This approach was initially based on the assumption that the culprit was *bacillus influenzae* or Pfeiffer's bacillus. Though many supported the bacillus as the cause of flu, this aetiological link was never completely secure. Doubts about Pfeiffer's claims surfaced in the decades before the 1918 pandemic, as bacteriologists in various parts of world failed to consistently isolate the bacillus from clinically defined cases of flu during sporadic outbreaks and epidemics.[17] British bacteriological investigations during the summer wave of the pandemic in the armed forces reinforced these doubts. While failing to isolate the bacillus, they found numerous other bacterial agents in uncomplicated cases of the disease.[18] This played havoc with the prospect of creating an effective flu vaccine and the War Office decided in early November 1918 to produce a combined vaccine from Pfeiffer's bacillus and other bacteria associated with secondary respiratory infections.[19] While somewhat effective against mild bronchial complications, this vaccine offered no protection against flu itself. In the eyes of British medical authorities, this undermined the specificity of Pfeiffer's bacillus as the cause of flu.

With evidence mounting against the bacillus, the War Office's Advisor on Pathology to the AMS, William Boog Leishman, called an emergency meeting with his colleagues at the MRC in early November 1918, and they decided to initiate the first British investigations into the possible role of a filter-passing virus in influenza The experiments would take place at military laboratories in Etaples, France and Abbeville, Flanders. The MRC supplied the teams with necessary equipment and materials, including experimental animals.[20] Within weeks, both groups claimed to have isolated filterable 'coccoid bodies' from sick servicemen and used them to produce 'experimental influenzal' lesions in the lungs of apes.[21] This work won support from Colonel S. L. Cummins, Advisor in Pathology to the British Armies in France, and leading London bacteriologists such as F.W. Andrewes, the respected Bart's professor of pathology and member of the MRC. But in a devastating critique of this work, J. A. Arkwright, known for his studies on the 'carrier problem', demonstrated that the alleged bodies were not pathogens, but either benign globoids or bacteria.[22] In Britain, as in other industrial nations, the matter of flu's aetiology plunged into controversy.

Although preliminary virus studies failed to solve the aetiological questions surrounding the disease, they succeeded in turning flu's viral identity into a genuine research problem. The possible connection between a filter-passer and the pandemic took on new meaning in the context of post-war reconstruction. Seen as part of the war effort, the struggle against the pandemic provided the MRC with a rationale for making virus research one of the cornerstones of its plans to modernize medicine.[23] Virus research fit well with Fletcher's vision of making basic research the necessary conduit through which to control the greatest health threats in modern society.[24] The pandemic had revealed flu as one such threat, and as it emerged as an important epidemiological and social factor in the interwar period, the disease presented a host of novel research problems for any virus worker venturing into this terrain.

Prior to the pandemic, flu was known to medical professionals and public health authorities as a potentially explosive epidemic disease, capable of affecting upwards of twenty-five percent of a population, but deadly for only a small number of the aged, infirm, and very young. Since flu's premonitory signs were notoriously vague, its incubation period short, and the speed of its spread unparalleled, medical authorities also knew that standard prevention measures were ineffective against the disease. Yet

until 1918, few worried about its ramifications for public health. Seen more as a nuisance than a threat, it was treated as one of the unavoidable maladies of modern life. The pandemic altered this picture irrevocably. Not only had flu's virulence changed, but so, too, had its pattern of mortality. Rather than killing the most vulnerable, it was men and women in the prime of life who accounted for the greatest number of dead. While features of the 1918 pandemic conformed to established knowledge of flu, its anomalies shook medical assumptions and the authority on which they rested.[25]

Up to 1918, British public health authorities approached flu prevention using an epidemiological model of the disease that had been constructed a quarter-century earlier. Large-scale investigations of a series of pandemics between 1889 and 1894, by public health bodies across Europe, including Britain's Local Government Board (LGB), established that flu was a contagious disease, caused by a specific microbe that spread from person-to-person.[26] But the complexity of flu epidemics and the sheer numbers left sick and dead during the pandemic were testimony that the state of knowledge was woefully inadequate to protect populations from the disease. Major Greenwood, one of London's leading epidemiologists, and the architect of the Ministry of Health's 1920 *Report on the Pandemic of Influenza*, admitted that the pandemic challenged the state of epidemiological knowledge far more than any epidemiologist could have anticipated.[27] Its scale and virulence raised doubts about simple causal models of infection and turned attention to multiple factors – including changes in the environment, changes in susceptibility, changes in the pathogen, or a combination of all three. These were all seen as factors responsible for flu's epidemiological variations and the rise and fall of epidemics.[28]

Notions of flu as a complex entity were hardly new. For clinicians, the pandemic confirmed an observation made in 1907 by the eminent British physician Sir Clifford Allbutt, Regius Professor of Physic at Cambridge University, that flu was 'of protean diseases the most protean'.[29] Clinical records stretching back to the eighteenth century, when the name 'influenza' first came into usage among English physicians, presented a clinically polymorphous disease associated with a stunning array of symptoms.[30] Beginning in the 1890s, British physicians constructed rather elaborate classificatory schemes to impose clinical order on the disease. By 1918, the general clinical picture presented in medical textbooks distinguished between uncomplicated (or simple) and complicated cases of flu. Uncomplicated influenza was defined as an acute disease, with an abrupt onset, severe prostration, and high (or continued) fever, accompanied by a range of constitutional symptoms, the most significant of which were racking headache, intolerable pain in the loins and limbs, and a dry cough. Uncomplicated cases were divided into three or four types: the respiratory, the gastric, and the nervous, and also sometimes the malignant. Physicians most commonly identified the respiratory form of flu, but the predominance of different types varied within and between outbreaks and epidemics.[31] Each type of influenza could morph into another, and turn into a more severe condition, usually of a respiratory kind. Complicated cases introduced an entirely new clinical picture, marked by bronchitis, tonsillitis, trachaeitis, and 'influenzal pneumonia', a deadly complication made notifiable in 1919.[32]

Despite clinicians' best efforts, flu remained a diagnostic challenge, a fact dramatically underscored by the 1918 pandemic. Flu emerged in entirely novel forms during the autumn wave, and physicians attending the worst cases in London hospitals were

overwhelmed not just by the numbers of in-patients, but by the severity and complexity of symptoms.[33] Most striking were complications associated with heliotrope cyanosis, a condition associated with influenza pneumonia in which volumes of mucous filled the alveoli of the lungs. As patients slowly suffocated, their lips turned blue and their complexion a pallid grey.[34] A sign of imminent death, the combination of pneumonia and heliotropic cyanosis claimed tens of thousands of lives. A key problem for clinicians was that they lacked a pathognomonic sign from which to make a clear-cut diagnosis of flu, so they were always negotiating through a complex symptomatology. Bacteriologists had been trying to establish a specific pathogen as a diagnostic marker for flu since 1890. But doubts about the status of Pfeiffer's bacillus and claims for other candidates, including a filterable virus, meant that laboratory-based definitions of flu had little bearing on clinical practice.

The variety of deadly cases and the scores of uncomplicated ones during the pandemic also highlighted the elusive nature of flu immunity. By 1918, physicians knew that a bout of flu provided little subsequent protection and, as a result, individuals were susceptible to repeated attacks of the disease. Just how often a person could catch the disease and the factors involved in their susceptibility were matters of debate. While the idea that people of certain dispositions or poor constitutions were at greater risk of the disease had been popular in the 1890s, this idea lost favour in 1918 as the disease swept away healthy young men and women.

By thrusting the disease into public consciousness and illuminating it as a serious national threat, the medical challenges posed by the pandemic changed flu's clinical and social visibility.[35] The experience of the pandemic became a prism through which understandings of flu were shaped in the 1920s.[36] Epidemiological, clinical and aetiological questions took on new significance as flu's identity was now intimately connected to the pandemic.

Flu could be no longer treated as an inconsequential medical problem. It came to occupy a central place in the social experience of health and disease in interwar Britain. The country was struck by four major epidemics in 1922, 1924, 1927 and 1929, while minor epidemics occurred in almost every other year (See Figure 6.1). Among infectious diseases, only diphtheria and scarlet fever accounted for greater levels of annual morbidity. Although flu rarely killed on its own, complications associated with it produced high levels of mortality. Between 1926 and 1929, 'influenzal pneumonia' accounted for the greatest annual levels of mortality among infectious diseases, killing, on average, nearly ten times more people than diphtheria or measles (See Figure 6.2). The North Riding physician, William Pickles, famous for his epidemiological studies in Wensleydale in the 1930s, described flu as the 'commonest and most important' infectious disease in modern Britain.[37] This perception was reflected in the experience and attitudes of medical practitioners, patients, politicians, and the press. Flu typically ranked highest amongst cases reported by general practitioners and highest amongst patients' complaints.[38] Physicians used flu as a catchall for various idiopathic respiratory, gastric and nervous conditions. In popular discourse, 'the flu' referred to an array of ailments, from fevers and colds to pneumonia. For government and the captains of industry battling constant economic crises, the disease mapped onto interwar anxieties over economic efficiency and social organisation. A *Times* editorial in 1928 captured contemporary worries: 'At more or less regular intervals influenza breaks out and

marches across the world, claiming millions of victims and causing grievous dislocation of human enterprise. Immense sums of money are spent on sickness benefits and on the care of the sick, and heavy losses are incurred by the majority of industrial undertakings; while numberless men and women lose their health permanently and become dependent on others....'[39]

	1920	1921	1922	1923	1924	1925	1926	1927	1928	1929
England	28.2	23.7	56.3	22.0	49.0	32.7	22.9	56.7	19.6	73.4
Germany	96.0	27.2	64.2	38.8	23.5	22.4	25.8	46.3	19.4	57.5
USA	70.9	11.4	31.2	44.3	19.4	29.7	40.8	22.6	45.3	55.5

Figure 6.1 Annual Flu Mortality Rates per 100,000 in England (Wales), Germany, and the USA, 1920-1929. Source: Z. Deutschman, 'Trends of Influenza Mortality During the Period 1920-1951', *Bulletin of the World Health Organisation*, **8**, 1953, p. 636.

	1926	1927	1928	1929
Influenzal Pneumonia	32,339	37,242	31,014	43,846
Diphtheria	2,994	2,732	3,191	3,446
Measles and German Measles	3,518	3,642	4,314	3,419

Figure 6.2 Deaths in England and Wales from the three leading notifiable infectious diseases, 1926-1929. Drawn from data compiled in the Eleventh Annual Report of the Ministry of Health, 1929-1930. London: HMSO, 1930, p. 30.

Concerns about a possible recrudescence of the 1918 pandemic, along with the impact of annual epidemics and outbreaks, kept flu in the public purview. The evident failure of modern medicine and laboratory science to control the disease prompted calls for, and the development of, new research efforts into its aetiological, clinical and epidemiological features. It was in this context that the MRC began putting together the pieces of its virus research scheme.

A Scheme for Virus Research

At the time of the pandemic, little was known about the basic nature of viruses. Having only emerged as research objects in bacteriological laboratories at the turn of the century, viruses were operationally identified as pathogens that were neither retained by standard bacteriological filters nor visible by methods of light microscopy.[40] Because

most pathologists at first assumed that filter-passers were susceptible to cultivation in ways similar to bacteria, filterability functioned as the key criterion of classification.[41] A 'filterable virus' was defined as a causative agent when clinical material that was passed through the smallest of available filters still induced disease in a host.[42] On this basis, a number of important human and animal diseases – including smallpox, rabies, foot-and-mouth, measles and poliomyelitis – had been classified as 'virus diseases' in the decades before the First World War.[43] The new category became popular among some experimental pathologists and bacteriologists as a way to explain the wide range of diseases for which specific causes could not be ascertained by standard bacteriological methods. Virus workers used 'filterable viruses' as professional levers for expanding the disciplinary bounds of bacteriology to include pathogens not classified as bacteria.[44]

The MRC started assembling the necessary institutional supports for a 'scheme of research' on the filter-passers in late 1922.[45] The NIMR, already designated as the MRC's central research laboratory, was made the hub of the programme. Situated in the London suburb of Hampstead, the institute occupied the buildings of Mount Vernon Hospital, a sizeable four-story structure, which the MRC had purchased in 1914 (See Figure 6.3). Fletcher and the NIMR's director, Henry Dale, reckoned that virus research would put the institute at the cutting-edge of medical science, making it and the Rockefeller Institute for Medical Research (RIMR) in New York the only two institutes in the world specializing in this nascent field.

The NIMR's virus programme aimed to develop basic knowledge and tools for elucidating the fundamental nature of viruses and virus diseases.[46] The strategy was to

Figure 6.3 National Institute for Medical Research – Hampstead (Front View). Source: Charles Harrington, 'The work of the National Institute for Medical Research', *Proceedings of the Royal Society of London*, 136, 1949, p. 348.

build the NIMR's expertise on established research lines. The MRC decided that the institute first concentrate on diseases that might best serve as models for the general development of virus research.[47] Measles, mumps and the common cold were selected from among human diseases, while dog distemper was selected from among animal diseases. Though the choice of dog distemper seems peculiar for an institute mandated for work on human diseases, Fletcher's explanation for it is revealing. Dog distemper's apparent analogies with influenza, he claimed, made it 'peculiarly suitable for working out methods by which human diseases of this class might be subsequently investigated'.[48] Dog distemper represented an indirect way to address the 'influenza problem'. Fletcher spelled out this rationale in his 1922 Annual Report:

> There is good reason to think that [dog distemper] offers a close parallel to human influenza. It seems probable that the infective agent is a filterable virus, and that here also the severity of the resulting disease depends largely upon secondary infections, facilitated by the primary infection. There is ground for hope that the study of dog's distemper under strict experimental conditions may throw important light upon analogous problems of human disease, and at least suggest new clues for investigation or new technical methods for the investigator. It is with the primary object of gaining knowledge of human disease that the Council decided to support further study of distemper in dogs.[49]

Whether used as a rhetorical appeal or part of a prescient research vision, influenza figured into NIMR's virus programme from the start.

The programme itself reflected important aspects of the kind of scientific modernism Fletcher and the MRC wanted incorporated into interwar medicine.[50] Fletcher and Dale framed viruses and virus diseases as complex scientific problems that no specialist could tackle alone. When they set out the institute's scheme of virus work, they stressed the importance of combining expertise from the physical, chemical and pathological sciences. Devised on the principle of teamwork, this approach presupposed institutional arrangements that not only brought together workers from disparate scientific fields but facilitated interaction so that ideas, methods and materials could be productively exchanged.[51]

The institute's Department of Experimental Pathology and Bacteriology was home to the programme. Initially comprised of a small nucleus of experimental pathologists directed by S.R. Douglas, a one-time student of Almroth Wright and a key figure in the MRC's war effort, and a tiny division of Applied Optics run by J.E. Barnard, an enigmatic West-end hatter and part-time physicist who pioneered methods of ultraviolet light microscopy, the department grew with the development of virus work. Patrick Laidlaw was recruited in 1922 to expand the virus programme. A respected Cambridge-trained biochemist and pathologist, who qualified in medicine at Guy's Hospital in London, Laidlaw had collaborated with Dale at the Wellcome Physiological Laboratories in the early 1900s on studies of the actions of histamine, before being appointed to the William Dunn lectureship in pathology at Guy's in 1913. Preferring the bench to the office desk, he embraced the opportunity to work directly on establishing the experimental foundations for virus research at the institute.[52]

Laidlaw's main object of study through the 1920s was dog distemper. It was with this disease that he made his mark in virus research and shaped the NIMR's approach to virus diseases. Laidlaw's distemper work received financial support from *The Field*, a

Figure 6.4. Mill Hill 'Farm' Laboratories,
Dog Distemper Isolation Compound.
Entrance and disinfection house is at the
left corner. A kennel maid's bungalow is
in the foreground, behind the tree, with
the kennels in the background. Source: P.P
Laidlaw and F.W. Dunkin, *A Report upon
the Cause and Prevention of Dog Distemper*,
London: The 'Field' Distemper Fund, 1928,
p. 12.

Figure 6.5 Mill Hill, Animal Hospital. Source:
Laidlaw and Dunkin, *Report …*, p. 14.

Figure 6.6 Mill Hill, Laboratory. Source: Laidlaw
and Dunkin, *Report …*, p. 13.

magazine for the 'country gentleman', whose readers included dog breeders and owners whose animals were regularly ravaged by this deadly canine disease. *The Field*'s 'Dog Distemper Fund', administered by a research committee, helped build a new research facility at Mill Hill, north of Hampstead.[53] Completed in 1924, the 'Farm Laboratories' provided a site for the breeding and housing of dogs and ferrets used in the work, and a well-equipped laboratory (See Figures 6.4, 6.5, and 6.6). The facility enabled Laidlaw and his colleague, F.W. Dunkin, to carry out extensive clinical and pathological studies on the disease. Collaborating with Barnard and the physicist, William J. Elford, who had joined Barnard's division in 1925 and devised new methods of virus filtration using collodion membranes, Laidlaw and Dunkin isolated dog distemper virus in the ferret, established its size, photographed it, characterized its pathogenesis in dogs and ferrets, and elucidated the nature of the immunity it induced. [54] By 1928, they had developed methods for producing a virus vaccine. Dale described the research as an exemplar of 'a complete and systematic investigation of a virus disease', and its culmination in the large-scale production of a vaccine in 1931 made it a symbol of the efficacy of the NIMR's style of virus research.[55]

Virus research at the NIMR was moulded around two lines of work. The first drew on physical and biochemical methods to create instruments and techniques for exploring the fundamental nature of viruses. The second, exemplified by Laidlaw's research, aimed to create 'immunological devices' for the identification and control of virus diseases.[56] Familiar to any bacteriologist, these devices included serological assays, therapeutic sera, and vaccines. Used with varying degrees of success on a number of virus diseases before the First World War, they were a standard part of virus research in the 1920s. Both research lines were critical to the NIMR's virus programme, but in the first instance viruses and virus diseases were approached as immunological problems best solved by immunological tools and techniques.

Partly reflecting virus work's connection to medical bacteriology, the use and role of immunological techniques took a form that was specific to the special demands of viruses and virus diseases. This was particularly true of the means employed to establish viruses as causative agents. Since these entities resisted cultivation in artificial media and visualization by light microscopy, interwar virus workers had two ways to demonstrate their presence in a disease. Viruses were made visible either by inducing an experimental disease in a susceptible animal or by tests for serum antibodies in convalescent animals or patients.[57] Serum antibodies were treated as crucial evidence in establishing the aetiological role of a virus. Immunological tests were thus essential to the elucidation of a disease's virus identity. The prominent American virus researcher, Thomas Rivers, described the pursuit of viruses and virus diseases as uniquely dependent on 'the science of immunology'.[58] Yet unlike bacteriologists, who had developed sophisticated serological assays with a variety of antibodies, virus workers relied heavily on one group of antibodies for their immunological evidence – the so-called neutralizing antibodies.[59] Based on an *in vitro* reaction between virus and antibody that was measured by the inactivation of the pathogenic effects of a virus in a research animal, virus neutralization tests defined approaches to what contemporaries called 'virus immunity' and shaped ways of working with and knowing viruses and virus diseases.

Virus Neutralization

Neutralization was a concept and technique intimately linked with the origins of modern immunology. When the Berlin bacteriologists Emile von Behring and Shibasaburo Kitasato discovered in 1892 that a serum substance – so called 'antitoxin' – inhibited diphtheria toxin, they illuminated a key immune reaction that paved the way for the late nineteenth century explosion in serum therapy and the development of humoral theories of immunity.[60] Embraced as a key property of immunity, the mechanism of neutralization emerged as a defining research problem in immunology. The American bacteriologist, George Sternberg, first used the term 'neutralization' in 1892 to describe how a soluble substance in the serum of immune cows inhibited the pathological effects of vaccinia.[61] A chemical term that referred to the reaction between acids and alkaloids, Sternberg used neutralization to denote the ability of a serum substance 'to destroy the specific virulence of [a] virus, when it contacts it'.[62] Paul Ehrlich, working on the standardization of diphtheria antitoxin in that late 1890s, developed his side-chain theory to explain this mechanism.[63] Describing neutralization as the irreversible union of toxin with antitoxin, Ehrlich argued that humoral immunity depended on the production of 'neutralizing antibodies'.[64] The quantitative methods Ehrlich developed to assess diphtheria antitoxin made neutralizing antibodies indispensable serological tools.[65] By first determining a consistent unit – the minimum lethal dose –of a toxin that killed a guinea pig, he measured the 'neutralizing power' of an anti-serum by injecting dilutions of toxin and serum mixed *in vitro* into the susceptible animal. Neutralization was identified when 50% of the animals survived. This method made it possible to quantify the amount of neutralizing antitoxin in a serum sample and to produce standardized antiserum. Ehrlich's quantitative work demonstrated how neutralizing antibodies could be harnessed for serological tests and serum therapies for different bacterial diseases.[66]

By the late 1920s, neutralizing antibodies were also becoming closely identified with virus work. They had been discovered in a number of virus diseases and neutralization tests were used in work on poliomyelitis, smallpox, vaccinia, measles, herpes and yellow fever.[67] F.M. Burnet summarized the basic methodological principles behind such tests in his influential review of *Immunological Reactions in Virus Diseases*:

> [Virus neutralization tests] all take the form of the inoculation of mixtures of virus and antiserum into tissue of a susceptible animal. The effect of antiserum is judged by the nature and extent of the lesions that develop in the animal after some convalescent arbitrary period [*sic*], in comparison with those produced in the absence of serum. The species of animal and particular tissue used for inoculation both play an important part in determining the result of inoculation of serum-virus mixtures … Neutralization of virus is … synonymous with suppression of a macroscopic … lesion.[68]

The histological lesion or the death of a laboratory animal served as an endpoint for neutralization. The tests were specific to the virus disease for which they were developed. They varied according to the animal, serum-virus mixture, inoculation technique, and endpoint used. The specific action of neutralizing antibodies in protecting against the pathogenic effects of viruses made them valuable diagnostic and therapeutic tools. No laboratory working on virus diseases could operate without them.

At the NIMR, neutralization tests were part of the practical work of identifying viruses, measuring serum antibodies and investigating the extent of immunity associated with vaccination and serum therapy. Serum quantification methods already figured centrally in the institute's work on setting national standards for biological substances, and Laidlaw's distemper studies demonstrated their usefulness for virus research.[69] Neutralization tests also constituted the main focus of NIMR workers' investigations into the nature of virus immunity, then considered one of the most important issues in virus research. Andrewes and Smith were recruited in 1927 to explore this problem, and they contributed to establishing the neutralization reaction as the key to understanding virus immunity.

Virus immunity was a lightning rod for controversy in the 1920s.[70] Early workers had claimed that virus immunity differed from bacterial immunity in both its duration and basic mechanism. This generalization derived from experience with a small sample of virus diseases – particularly poliomyelitis, smallpox and vaccinia – in which viral infections were known to induce highly specific and long-lasting immunity rarely seen in bacterial infections.[71] For some, this suggested that the underlying mechanisms of virus immunity depended less on the action of serum antibodies than on changes in tissue. The Pastorian, Constantin Levaditi, was a vocal proponent of the centrality of cellular immunity in virus diseases.[72] Virus workers like Thomas Rivers and the young Jonas Salk found support for this view in the increasing evidence that viral infection was a fundamentally intracellular process.[73] Even a sceptic, like the eminent bacteriologist, W.W.C. Topley, acknowledged that, 'it seems very possible that this habit of [viruses] functioning as intracellular parasites has an important bearing on antiviral immunity'.[74] However, while many researchers accepted the possible role of cellular immunity, the preponderance of work on this problem aimed to bring virus immunity into accord with dominant humoral models. Elucidating the mechanism of virus neutralization was key to this project.

Early workers claimed that the mechanism was analogous to the action of bacteriolysins against cholera vibrios, such that neutralizing antibody acted liked a 'virucide'.[75] This explained solid immunity observed in diseases like vaccinia, but it failed to account for why in other virus diseases –such as herpes simplex – immunity appeared to be short term or transient. These cases suggested that neutralization operated on a principle other than lysis, and by the late 1920s virus workers were trying to determine this principle.

The problem preoccupied Andrewes when he started his career at the NIMR. After studying medicine and bacteriology at St. Bartholomew's hospital in London, where his father, F.W. Andrewes, was a leading pathologist, he spent two years training at the Rockefeller Hospital in New York, where he became familiar with immune reactions in virus diseases.[76] Vaccinia was then the model for studying *in vitro* antigen-antibody reactions in filterable viruses, and Andrewes used the disease for his work on virus neutralization. In 1928, he demonstrated that vaccinia virus and 'virus III' could be recovered from neutral serum-virus mixtures.[77] This contradicted early claims that neutralization destroyed the virus. Yet the presence of virus in immune sera also suggested that neutralization did not involve the strict union of antigen with antibody, but was instead reversible. Andrewes' claim was challenged by Samuel Bedson, a leading virus researcher at the London Hospital, whose work on herpes virus had shown that if a virus-serum mixture was allowed a period of contact *in vitro*, a 'slow union' occurred

between virus and virus antibodies.[78] When Andrewes re-examined the reaction between vaccinia virus and anti-vaccinial serum in light of Bedson's work, he revised his earlier claim and argued that while virus neutralization was based on a reversible antigen-antibody union, virus immunity depended on the durability of this union.[79] Andrewes' studies effectively aligned virus immunity with established humoral models, and his conception of virus neutralization became a framework for approaches to virus immunity at the NIMR.

Virus neutralization held two promises for virus workers: *within* the reaction were the keys to the mechanisms of virus immunity; and *with* the reaction, they could make neutralization tests for identifying, tracking and controlling virus diseases. The first promise proved elusive. Hampered by technical constraints, it was not until the development of plaque and fractionation techniques in the 1950s that researchers could fathom the chemical bases of neutralization. Even then, virus neutralization remained a contested issue.[80] Neutralization tests thus functioned as tools without an agreed-upon theoretical explanation. This did not stop their development and use, yet making workable tests for virus diseases was hardly straightforward. As Burnet underlined, experimental animals were a necessary condition for their production, and this imposed an important constraint on their range of application.

The lack of a viable research animal foreclosed the experimental investigation of a number of suspected virus diseases, including flu. Through the 1920s, work on flu's virus identity was limited to the use of humans as experimental subjects. Inferences made from observational studies of the disease in humans had a long history, but these kinds of studies yielded few new insights into flu's cause, and provided little foundation for the development of vaccines or other forms of prevention. By the early 1930s, researchers had exhausted all the possible routes for studying flu in humans. Fletcher summed up the state of affairs:

> The prime difficulty is that no animal (except possibly the anthropoid ape) is affected by influenza … we might get … success with influenza if we could … use humans especially bred without any previous contact with influenza, who would submit themselves to experimental study. This of course is impracticable.[81]

The solution to flu's virus identity hinged on creating a workable animal model.

Ferret Flu

In the eyes of most medical authorities, the inability of laboratory workers to resolve flu's aetiology meant that medicine and public health were impotent against flu epidemics. 'The etiological problem presses for solution', noted W.W.C Topley and G.W.S. Wilson in the first edition of their authoritative textbook, *Principles of Bacteriology and Immunity*. 'For against epidemic influenza the public health administration is at the moment, entirely powerless…'[82] This worry was underscored by a dramatic epidemic in 1929, which summoned memories of the 1918 pandemic and lead to widespread demands for more concerted medical research on the problem. Since this was now the domain of the MRC, politicians, the press, and the medical profession looked to the Council for answers. Much attention concentrated on advances made in virus research and, particularly, the

success of Laidlaw's dog distemper work. '[T]he sad state of unpreparedness in which the world finds itself ought to awaken determination to discover, if possible, some means of prevention', argued the *Times* in late 1929. 'An effective approach to the problem', the editorial continued, had already been demonstrated with dog distemper: 'Is it too much to ask that work on similar lines should be undertaken in the cause of influenza? The work on distemper has opened a way; general studies organized by the Medical Research Council on virus diseases have made parts, at any rate, of that way smooth. Has not the time arrived to launch a campaign and to come to grips with the enemy?'[83] Public pressure on the MRC to act on flu came to a head in December 1932, when another epidemic struck London. Letters sent to the MRC and published in *The Lancet* and *BMJ* (*British Medical Journal*) demanded to know what initiatives the Council was taking.[84] Sir Halley Stewart, an important MRC patron, offered Fletcher the considerable sum of £2,500 to launch an 'Influenza Campaign'.[85]

Through the 1920s, the MRC supported flu research through grants to individual researchers at university laboratories, while at the NIMR, Laidlaw and his colleagues developed general expertise and techniques for studying filter-passers. This strategy paid dividends for the institute, making it a world-leading centre of virus research, but it bore little fruit in the battle against flu. With public pressure mounting, Fletcher and Dale decided that, with the NIMR now ready to tackle a complex disease like flu, the best strategy was to concentrate research in the hands of a small team of experienced virus workers. Laidlaw, who was about to be knighted for his dog distemper work, was put in charge of the investigations; Andrewes and Smith joined him as co-workers.[86]

Virology textbooks treat the NIMR's contributions as birth of modern flu virus research.[87] Much has been made of the remarkable speed at which the team succeeded in changing the material practices and meanings of influenza. Two crucial discoveries facilitated these changes: the first, credited to Smith and made only a month into the team's research, demonstrated that the ferret could be used for isolating a virus from flu patients; the second, made less than a year later, rendered the mouse into a tool for accurate neutralization tests. Though there is little doubt that these discoveries transformed laboratory work on flu, we should not forget the extensive labour that went into their production and legitimization. Ferrets and mice did not come ready-made for flu virus work. Resources and time had to be invested into making them into workable models and tools for flu research and into establishing their wider medical relevance. Flu's virus identity was the outcome of a long series of transformations that involved the creation of new social relations between the laboratory, clinic and public health.

When the NIMR workers started investigating flu in January 1933, their first aim was to tackle the vexing problem of creating an animal model of the disease. To do this they tested animals at the institute for their potential susceptibility to flu. Since the NIMR was not connected to the London hospital system, they relied on fellow pathologists at Guy's Hospital and St. Bartholomew's Hospital to supply them with nasal washings and lung samples from flu patients in their wards.[88] The team received samples from eight patients, including a young girl who had died of respiratory complications at Bart's. Smith injected filtered and centrifuged washings into rats, mice, guinea pigs, rabbits, monkeys, pigs, and horses.[89] These efforts failed. Curiously, the ferret was not among the first test animals, even though it had been part of the NIMR's laboratory ecology since 1926, when Laidlaw and Dunkin had introduced it as a model for dog distemper.

An Experiment in the Fight Against Influenza: A Ferret is Injected
Fluid infected with known or suspected influenza virus is dripped into a ferret's nose at Hampstead Laboratory. The ferret has previously been anaesthetised with ether.

Figure 6.7 Nasal injection of the ferret. Andrewes, holding the pipette, and an unknown assistant, holding the ferret, demonstrate the standard technique of 'instilling' virus material into the nose of a ferret. The ferret was anaesthetised with ether, to ease injection of the virus material. Source: Picture Post, 'Can We Beat Influenza?', 2 February 1946, p. 10.

The idea to test the animals was prompted by reports of an outbreak of a flu-like disease among ferrets at the Wellcome Physiological Laboratories, where the animals were being used to manufacture dog distemper vaccine. In early February, Smith dripped ('instilled') into two ferrets' noses filtered nasal washings taken from Andrewes, who had himself caught flu. Within forty-eight hours the animals started sneezing and displaying signs of a flu-like disease. Washings from seven other patients also induced the disease. But almost immediately the team lost the experimental disease – and the chance to isolate the virus – when distemper broke-out among the ferrets. By a twist of fate, Smith caught flu after the outbreak on 4 March, and this time, Andrewes used his washings (and his instillation methods) to infect a new batch of ferrets now maintained under strict quarantine at the Mill Hill facilities (See Figure 6.7). This work ultimately yielded the first flu virus – later designated 'WS' after Smith – which became the NIMR's master strain.

Stunned by their results, the team fashioned the ferret into a workable research animal through the spring of 1933, and started using it to explore longstanding research problems. The ferret enabled the team to isolate a filterable virus from the 'infecting material'.[90] The agent met established criteria: while the agent was filterable, invisible and could not be cultivated in standard growth media, it was also easily transmitted to ferrets, and the experimental disease could be reproduced in large numbers of animals through serial passage. Moreover, the agent could be neutralized with serum from recovered ferrets, as demonstrated by the inhibition of flu-like symptoms in treated animals. The last two techniques were especially important for virus identification. The reproduction of an experimental disease by 'serial passage' was a classic bacteriological technique for isolating pathogens, and interwar virus workers relied on it to make viruses visible in the form of lesions or other pathological changes in experimental animals. Serum neutralization tests represented the only other indirect method of visualizing a virus, and because of their presumed specificity, neutralizing antibodies were especially important for linking a virus to a disease. The credibility of both techniques, however, rested on workers' ability to delineate a typical and replicable experimental disease in a research animal. For these identification techniques to work for flu virus, the ferret itself had to be established as an animal model of human influenza.[91]

The fact the ferret was a familiar laboratory animal eased this process. Laidlaw's experience with the animal and the availability of a laboratory, animal house, and breeding and isolation facilities at Mill Hill enabled the team to devote their attention to turning the ferret into a flu model. Making an animal model involved a combination of the technical acumen needed to perform serial passage experiments and representational practices to render the experimental disease into a credible clinical entity. In the first six months of their research the team reproduced the experimental disease in over 135 ferrets and traced 'the full course of [the] illness' in 64 animals.[92] Serial passage enabled them to establish continuity in the illness' clinical picture, which they described in detail in their first report in the *Lancet* on 6 July 1933 and on various occasions thereafter. Laidlaw gave the following description to an audience at Guy's Hospital in summer 1934:

> [The disease in ferrets was] characterised by an incubation period of 48 hours, followed by fever, in which the temperature may rise as high as 107F. This is followed by a remission, and thereafter a second febrile period, usually lasting three or four days, during which there

are symptoms of severe nasal catarrh, such as sneezing, nasal obstruction… mucopurulent discharges from the nose, sticky encrustation round the nares, and so on. Throughout the illness, but varying considerably from cases to case, there is prostration and lethargy, and occasionally obvious signs of muscular weakness.[93]

Laidlaw called the disease 'experimental influenza'; in more vernacular settings, he and his colleagues preferred the term 'ferret flu'.[94] The names denoted significant analogies between the animal and the human disease, and this became an important rationale for using the ferret for studies of flu immunity and pathogenesis. Yet what mattered most at this stage was to show that ferret flu was the outcome of an experimental infection with human flu and the product of virus infection.

One way the team demonstrated this link was through fever charts. A standard representational device in clinical and veterinary medicine, the NIMR workers used fever charts to visualize the onset and progress of experimental infection, and to identify possible diagnostic markers for the presence of the disease agent. A hand-drawn chart published as part of the NIMR's report of their discovery in the *Lancet* details the production of ferret flu with human flu material (See Figure 6.8). From Andrewes' laboratory notes we know that the chart represents his inoculation of Smith's washings into a ferret ('F24') and traces the process of the experimental disease between 4 March and 4 April 1933.[95] Temperature readings from the ferret's rectum were taken every morning ('M') and evening ('E') from the outset of the experiment to its completion, when the ferret was returned to the ferret house for future immunological work. The chart presents readings up to 26 March, when the ferret started to fully recover. The first temperature spike, recorded on the morning of 7 March, preceded the onset of mild flu-like symptoms by a day. It marked the height of infection and, as the NIMR workers found out when they tested other ferrets, the point at which the virus was most concentrated in the animal and most easily recovered. The temperature spikes thus corresponded with the activity of the virus. Fluctuations recorded in the symptomatic
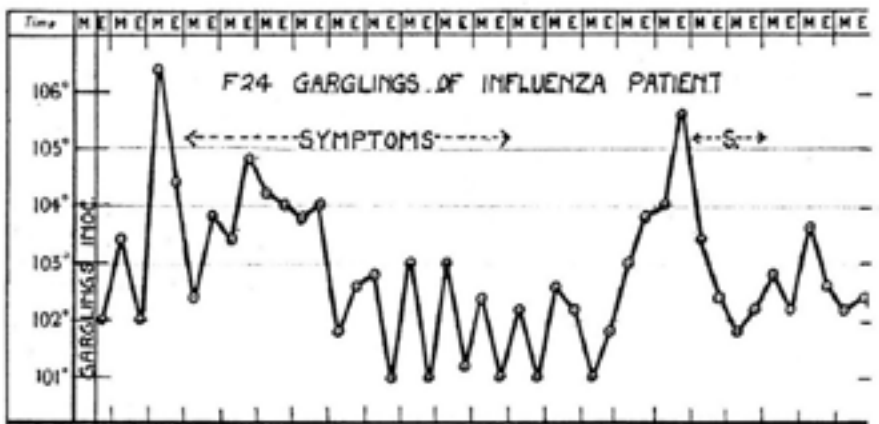

Figure 6.8 Ferret Flu - Fever Chart. Blank fever charts, such this one used for this data, were sold at chemists such as Boots. Source: W. Smith, C.H. Andrewes, and P.P. Laidlaw, 'A Virus Obtained from Influenza Patients', *Lancet*, 2, 1933, p. 67.

stages of the disease curiously resembled the 'continuous fever' long associated with clinical influenza in humans. The second temperature rise, two weeks later, announced a 'relapse' of symptoms ('S'). Although deemed somewhat unusual, such recrudescence was familiar to any clinician who had encountered flu.

As a form of visual evidence, the fever chart had many functions. Widely used in clinical medicine, it was readily legible to any physician, who could easily connect the production of ferret flu with the 'garglings of [an] influenza patient' and see the link being made between the experimental disease and the human disease. When allied with the team's descriptions of ferret flu, the chart also illuminated a process of infection that was analogous to that seen in flu patients. More generally, it placed the discovery of flu virus in a clinical format. This last point is especially important, for it was through the production of ferret flu that Laidlaw's team were able to develop a neutralization test to determine whether sera from their ferrets – and humans – contained antibodies that specifically neutralized the virus.

The ferret test was rather rudimentary. Neutralization was demonstrated when a dilution of ferret or human sera, and a fixed amount of virus mixed *in vitro,* protected a healthy ferret against ferret flu. A ferret infected with a virus-saline mixture was used as
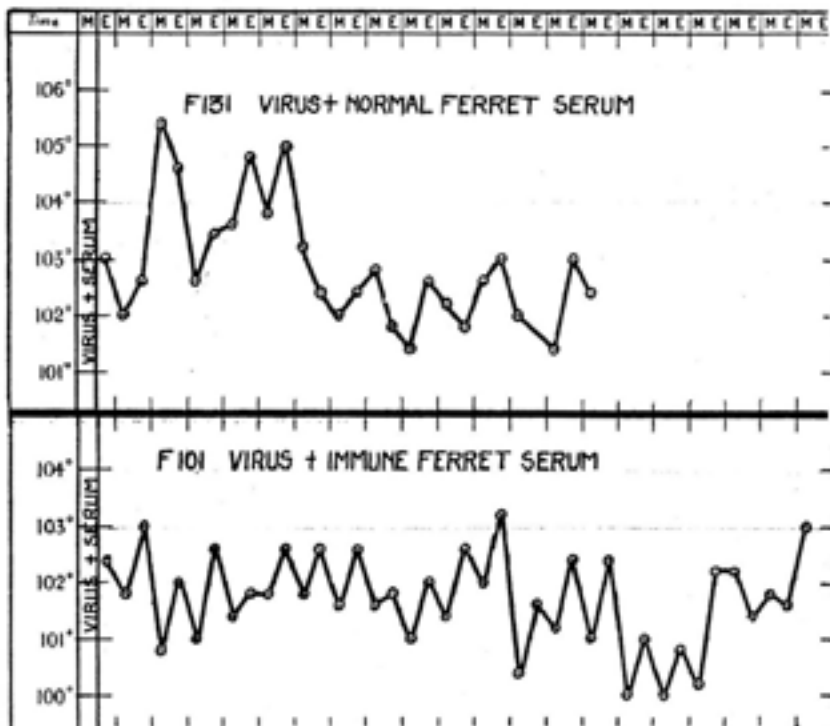

Figure 6.9 Ferret Flu – Neutralized. Upper chart – Ferret (F131) infected with a mixture of virus and normal ferret serum. Lower chart - Ferret (F101) infected with a mixture of virus and immune ferret serum. Virus neutralization is demonstrated in the lower chart. Source: W. Smith, C.H. Andrewes, and P.P. Laidlaw, 'A Virus Obtained from Influenza Patients', *Lancet*, 2, 1933, p. 68.

a control. The team established the specific relationship between neutralizing antibodies and the virus by comparing the 'neutralizing power' of ferret sera taken before infection, at the acute stage (within 48 hours), and during convalescence. While 'normal' sera taken before infection had little effect against the disease, convalescent sera contained potent antibody that inhibited the disease.[96] Two fever charts, also published in the discovery report, displayed the contrasting results of neutralization with and without immune serum (See Figure 6.9). When a mixture of virus and normal serum was instilled in a healthy ferret (F131) it produced the 'dysphasic' fever associated with ferret flu. Yet when a mixture of virus and immune serum was instilled in another ferret (F101), temperature readings never exceeded the normal range for the animal (between 101-103 degrees). Tracing the action of these antibodies on the 'virus', the lower chart showed how the neutralization test could be used for the indirect identification of virus infection, and indicated the specific relation of neutralizing antibodies to the disease.

Based on these results, the team evaluated human sera for neutralizing antibodies to Smith's virus. In March, Andrewes obtained serum samples from six Bart's nurses who had recovered from flu.[97] He mixed their sera with virus *in vitro* and inoculated the mixture into a ferret, while a control ferret was inoculated with virus alone. Like the convalescent ferrets, the nurses' sera neutralized the virus, although less thoroughly. Nonetheless, this was indication enough of a specific infection. If the antigen was indeed a virus, the neutralization test had been proven to be a tool for elucidating its presence in ferret and human flu.

Before publishing their research, Laidlaw and his colleagues collected a final piece of serological evidence. A standard method for corroborating the identity of a suspected virus was to see if it bore a serological relationship to known viruses. The NIMR workers reckoned it was worth comparing their virus with a virus isolated from pigs by the American veterinary pathologist, Richard E. Shope.[98] A leading animal virus worker at the Rockefeller Foundation's Princeton field laboratories, in 1931 Shope had determined that swine influenza – or 'hog flu' – was a dual infection, caused by a combination of *haemophilus bacillus (suis)* and a filterable virus.[99] Shope's discovery prompted speculation that an analogous type of infection might be the cause of human flu. Laidlaw was particularly interested in Shope's hypothesis, but his team's filtration tests had excluded 'visible bacteria' as viable agents in human flu.[100] What they did establish, however, was a close serological link between the two viruses. Andrewes had befriended Shope during his time in New York, and the two exchanged samples of their respective viruses. Shope sent the NIMR team his virus in a dried pig lung, while Andrewes returned the favour by sending Shope the WS strain in dried turbinate bones extracted from the nasal cavities of the experimental ferrets.[101] With Shope's virus, Smith and Andrewes produced a disease 'indistinguishable from the ferret disease caused by virus of human origin'.[102] Cross-immunity and cross-neutralization tests traced the link between the two viruses. Ferrets that recovered from the swine virus were 'solidly immune' to infection from the human virus. Ferrets convalescent from the human virus were partly immune to the pig strain. Cross-neutralization tests, in which a healthy ferret inoculated with a serum-virus mixture using one antigen was inoculated with the other antigen, indicated a relatively close antigenic relationship between the two viruses. While these tests offered only indirect evidence that ferret flu was a virus disease, the serological association with swine flu strengthened the case. 'The similarities completely outweigh the differences',

explained Laidlaw to an audience at Guy's Hospital a year later. '[W]e consider that the results with the human strain of virus coupled with those obtained with swine virus are strong arguments for the view that influenza in man is primarily a virus infection'.[103]

The team's decision to publish its first report in the *Lancet* on 8 July 1933 had important ramifications for the profile of their discovery work. Though the *Lancet* and the *BMJ* carried research on virus diseases, most experimental virus work was published in the *British Journal of Experimental Pathology*, a specialist venue rarely read by physicians. The *Lancet* was, by contrast, one of the flagship journals of the medical profession. Targeted at the average practitioner and clinician, it was a key forum for vetting and highlighting important medical issues and developments for the profession and the public. Publication of a discovery in the *Lancet* was thus a powerful form of legitimization. Aware that their claim to the discovery of a flu virus was not the first of its kind, Laidlaw's team needed the organs of medical press on their side. '[T]he evidence', they argued, '…strongly suggests that there is a virus element in epidemic influenza, and we believe that the virus is of great importance in the aetiology of the human disease'.[104] But the strength of their new experimental animal, methods, or research skills alone could not sustain this discovery claim; it also depended on the support it received from the medical and lay press, which acted as important conduits for the wider sanction of flu's virus identity.

The report caused a minor media sensation in London. The *Lancet* editorialized that the NIMR's work had put flu research on a new footing: 'It is almost impossible … to over-estimate the importance of the discovery … that the ferret is susceptible to infection with human influenza'. The NIMR workers had 'offered almost conclusive evidence that the primary cause of human influenza is a filterable virus'.[105] The *BMJ* weighed in with a similar declaration: 'Just when the possibility of any further advance seemed rather remote, three investigators at the National Institute for Medical Research … succeeded in transmitting influenza to ferrets. The whole aspect of the situation has been transformed'.[106] *The Practitioner*, journal of London's physician elite, concluded that 'the results with ferrets, as far as they have gone, are consistent with the view that epidemic influenza in man is caused primarily by virus infection.'[107]

Having received the team's report a day before its publication, London's lay press translated it into a resounding victory for medical science.[108] The *Daily Telegraph*, which had promoted Laidlaw's dog distemper research, ran the discovery as a lead story on the same day. It devoted its front page and two columns to describing the '40 Years' Search For The Cause of Influenza' and 'How the virus was tracked down' at the NIMR (See Figure 6.10). Smith, Andrewes, and Laidlaw were identified as 'British Doctors', doing work of immediate practical relevance, rather than as scientific boffins working outside the realms of everyday medicine (See Figure 6.11). Readers were reminded of how 'the practical outlook looked gloomy' in the 1920s and how many thought '[v]ast epidemics might sweep the world again and mankind would again be the helpless victim of the spreading scourge'. The NIMR's use of the ferret to 'show that a virus is the true causative agent [of the disease]', changed this picture. 'It is now certain that real progress is being made'.[109]

The ferret's sneeze became an icon of the power of medical science. Particular attention was drawn to how, as the *Daily Telegraph* put it, 'the serum of human convalescents was capable of neutralising the virus of the ferret disease'. [110] Laidlaw and his colleagues

Figure 6.10 Discovery in the News. Source: *Daily Telegraph*, 7 July 1933, p. 10
Figure 6.11 'Primary Cause of Flu Isolated'. Source: *Daily Telegraph*, 7 July 1933, p. 7

had suggested that virus neutralization and immunity in ferrets might have important application to the problem of flu immunity in humans. This suggestion was interpreted through broader notions about 'neutralization' linked to successes of serum therapies developed for diphtheria, typhoid, tetanus, and measles.[111] In the age of serology, neutralization resonated with images of medical control over infectious disease.

The ferret revolutionized flu research. Within a year, Shope reproduced the team's ferret work, and Thomas Francis Jr. and his co-worker, Thomas Magill, at the Rockefeller Institute, used the ferret to isolate a virus strain from clinical samples taken from an outbreak in Puerto Rico.[112] Ferrets immunized against their new strain (PR8) were also immune to the NIMR's WS strain; and sera for one virus neutralized the other. By 1935, workers in Melbourne, Leningrad, Philadelphia and Manchester had developed variations of the NIMR's ferret system.[113] This ferment of work forged new links between laboratories and went far in consolidating the ferret as an animal model of flu. Yet turning experimental work into applied medicine was more difficult than its replication in other labs.

The NIMR's first move towards the wider application of the research began in late 1934 with a study of 'the antibody content of normal sera' in Londoners aimed at addressing the problem of flu immunity.[114] Neutralization tests in ferrets demonstrated that some Londoners had antibodies to both the WS strain and Shope's swine influenza. The tests also indicated that neutralizing antibodies increased in ferrets during convalescence and that convalescent serum 'enhanced waning' immunity. This suggested that a correlation might exist between changing antibody levels and levels of flu immunity. The question of whether these changes were linked to individual susceptibility and the rise and fall of flu epidemics had preoccupied physicians and epidemiologists since the 1890s. If what the team found in ferrets was applicable to humans, they believed they could devise protective serum therapies or vaccines against flu.

To pursue this line of investigation, the team developed a 'reference' antiserum against which to evaluate antibody levels to WS virus. Produced by hyperimmunizing horses with flu virus, the efficacy of the antiserum depended on the team's ability to measure its neutralizing power. This involved testing serial dilutions of a serum mixture to a specified endpoint – either the production of a discrete lesion or death in a research animal. The standard measure for the quantification of all serum tests defined the endpoint for final dilutions at 50% (LD50), in which equal numbers of animals inoculated with serum virus mixtures showed, or did not show, lesions characteristic of a virus.[115] Ferrets were poor animals for this kind of work. They were expensive to breed, produced small litters, and demanded complex isolation and housing facilities. Moreover, 'ferret flu' manifested as a non-lethal respiratory infection, without a distinct lesion. It was therefore impossible to isolate a pathological marker against which to quantify the antiserum.[116]

Recognizing these practical limitations, the NIMR workers searched for a more suitable animal. In early 1934, Smith at the NIMR and Francis and Magill, who had moved to the Rockefeller Foundation's International Health Division (IHD) laboratories in New York, simultaneously devised a method for transmitting 'ferret flu' virus to mice.[117] The pathological picture produced in the mouse was key to the animal's transformation into a serological tool. Serial passage of the virus induced 'plum-colored' lung lesions, the consolidation of which killed the animals.[118] These lesions could

be modified by changing virus-serum mixtures and, for the NIMR team, were good markers for calibrating the potency of their horse serum, which they called 'IH2'. In a series of experiments in late 1934, the team compared the effects of increasing five-fold dilutions of IH2 and sera from convalescent and previously uninfected humans, mice and ferrets. As expected, different dilutions provided different levels of protection against lung lesions. The team determined the neutralizing power of serum dilutions in correlation with the resolution and consolidation of mouse lung lesions observed *post mortem*. While convalescent human sera protected the animals against the disease, IH2 proved to be a more potent antibody, neutralizing virus at equal or greater dilutions. Though IH2 did not completely prevent infection, it inactivated the virus enough to protect the animal from developing lung lesions. This was a crucial piece of work, serving as a building block for the mouse neutralization test and the potential therapeutic uses of IH2.[119] The mouse test not only enabled the NIMR workers to measure the potency of their horse serum, but it gave them a way to more accurately detect and compare the presence of neutralizing antibodies in human and animal sera for diagnostic or epidemiological purposes, and to distinguish different virus strains.

When the team reported their work in the *Lancet* in October 1934 they hoped that the mouse would provide a 'readily available' method for detecting influenza virus.[120] The medical and lay press seized on this idea. 'With such an easily handled and inexpensive animal as the mouse available for work on influenza', noted the *BMJ* '…this line of research comes within the scope of most laboratories'[121] This was jumping the gun. Try as they might, the NIMR team could not induce infection in mice with human nasal washings Mice appeared to be susceptible only to virus first passed through ferrets. The promise of simplifying laboratory diagnosis would have to wait. Instead, the value of the mouse derived from its use as a serological tool for exploring the complexities of flu immunity.

Putting Mice to Work

Up to October 1934, the NIMR workers had elucidated the properties of flu virus infection in ferrets and mice. Their evidence had yet to establish a certain identity between flu in their animal models and flu in humans. The research problems the teams tackled over the next five years attempted to resolve this question and to demonstrate the practical relevance of the research. Using their new neutralization test as a key investigative tool, their strategy was to concentrate on three interrelated problems: the relationship between neutralizing antibodies and human immunity to flu, the clinical identity of epidemic influenza, and the development of a flu vaccine. This strategy also required extensive collaboration with London pathologists and physicians, and it drove the NIMR's initiative in 1936 to link together laboratory and clinical investigations of flu in the metropolis.

The seeds of the collaborative investigations had already been planted by the team's preliminary serological work, but their importance grew when they started to put the mouse test to work on a comprehensive serological study of flu antibodies in 1935. By tracking the incidence and comparing the neutralizing power of antibodies in Londoners for the WS virus strain and Shope's swine virus, the team wanted to know whether a relation existed between changing antibody levels and immunity, and

whether these changes were linked to the rise and fall of flu epidemics.[122] While these questions had long preoccupied epidemiologists, the NIMR workers believed the mouse neutralization test provided them with a tool to test these connections in the laboratory. Through 1935, they collected sera from hundreds of Londoners of varying age groups. London hospitals and medical officers at public schools supplied the bulk of sera from children; medical workers in the United States sent a number of adult samples; and finally, military instillations provided considerable quantities of serum from servicemen of various ages. Constrained by the costs and time it took to run neutralization tests, they fully examined the sera of 113 individuals for serum antibodies to WS virus and swine flu virus.[123] Identifying 'neutralizing antibodies to human (WS) influenza virus… in the majority of human sera examined', their assessment yielded the first serological picture of the distribution of flu virus in Londoners (See Figure 6.12).[124]

These graphs were a striking demonstration of the use of neutralizing antibodies as evidence in support of the link between WS virus and human flu. The antibodies were deemed key traces of the presence of flu virus infection in a cross-section of Londoners. The identification of swine flu virus antibodies marked the beginning of serological work that lead to Shope's infamous claim that the 1918 pandemic was a zoonotic disease caused by swine flu virus. The practical implications of this work were readily apparent. The incidence of these antibodies in the population suggested that flu infection conferred some kind of immunity, the history of which could be traced serologically.

Since it was well known that flu epidemics waxed and waned seasonally, it was important to determine whether changes occurred in antibody levels over time. When the team tested a sample of Londoners again in early 1937, their antibody levels had dropped considerably, in some cases to the point where they could not be identified. That summer, at the annual meeting of the British Medical Association, Andrewes speculated that, 'knowledge of such variations might … give … insight into one of the factors controlling the periodicity of influenza epidemics'.[125] His prediction seemed to be confirmed when, after a large flu epidemic exploded in London that autumn, antibody levels shot up again. But while the team's serological studies were pointing to the potential epidemiological and clinical significance of neutralizing antibodies, their clinical value would remain unclear until the team correlated a specific clinical entity to the virus and antibodies they had identified. This was important not just for consolidating flu's virus identity, but also for targeting vaccines and antiserum.

Stuart-Harris described the challenge they faced at the time: 'It was apparent that a satisfactory application of such [laboratory] methods to human beings must largely depend upon the possibility of demarcating cases of influenza of virus aetiology from other diseases with similar symptoms. Correlated clinical and laboratory studies were clearly necessary'.[126] It was around this necessity that the team organized its collaborative investigations.

The main sites for the studies were hospitals at military garrisons in and around London, while smaller scale studies were carried out at non-military hospitals. Military hospitals provided relatively uniform and more easily controlled populations. And because of the MRC's ties with the Army Medical Services, military populations were also more accessible to the NIMR workers. Nonetheless, creating a stable network of relations with civilian and military clinicians and pathologists was a crucial part of the NIMR's research. During suspected flu outbreaks in late 1936 and late 1937 the
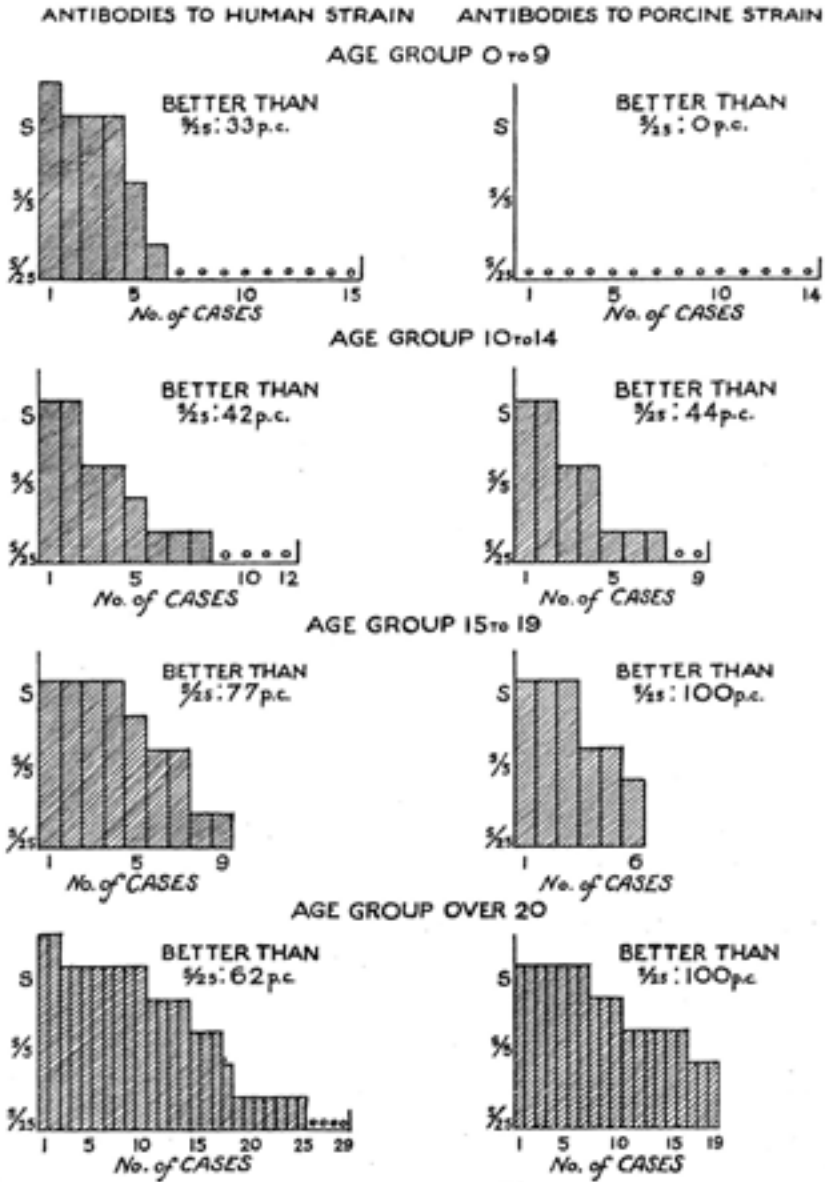
Figure 6.12 Neutralizing Antibody Levels in Londoners. Each vertical column represents a serum. The height of shading indicates the quantity of antibody in the serum. Sera were graded as better than S (standard IH2 or IH4 horse-antiserum), equal S, S/5 (one-fifth the neutralizing power of S), or S/25 (one twenty-fifth the neutralizing power of S). Spaces marked O indicate sera with no antibody or with less than S/25. Source: C.H. Andrewes, P.P Laidlaw, and W. Smith 'Influenza: Observations on the Recovery of Virus from Man and on the Antibody Content of Human Sera', *British Journal of Experimental Pathology*, 26, 1935, p. 577.

team worked with pathologists to collect masses of nasal and throat garglings for their work. The *Daily Herald* conjured a war-like image of the team as 'flying squads' moving between their Hampstead laboratory and hospitals in the search for a 'cure'. But forging such links was more mundane.

Much of this work fell to Stuart-Harris. He joined with hospital physicians to make detailed clinical notes on patients and personnel entering wards with flu-like symptoms.[127] Part of his job was to characterize cases from which virus was isolated, with the aim of developing a specific clinical picture of the disease. Samples collected from these patients were sent to Smith and Andrewes at the NIMR to be tested for virus in ferrets. Serum samples were taken to test for the presence and levels of antibodies. The NIMR workers attempted to carve out a specific 'virus disease' by correlating the recovery of virus in ferrets with a particular clinical picture in humans. Stuart-Harris compared clinical notes from the 1936 flu outbreak, from which virus was not isolated, and the 1937 epidemic, from which it was regularly isolated. In a widely publicized report published by the MRC in 1938, he distinguished 'febrile catarrhs', which encompassed a cluster of respiratory conditions of unknown aetiology, from 'epidemic influenza', a specific clinical entity aetiologically linked to the virus.[128]

The mouse neutralization test took on particular importance in this work. In the laboratory, Andrewes and Smith determined that in cases identified as 'epidemic influenza', serum from convalescent patients 'acquired very definite neutralizing powers', while by contrast, 'no such neutralizing powers appear[ed] in the sera of patients suffering from respiratory diseases other than influenza'.[129] The mouse neutralization test thus became a tool for the retrospective diagnosis of 'epidemic influenza'. This was especially important since the test enabled the team to evaluate the efficacy of an experimental flu vaccine they had made in late 1935 from mouse lung virus inactivated by formaldehyde.[130]

The production of the vaccine highlights how the NIMR workers moved between their animal models and human flu. In their laboratory experiments they found that the immunity conferred by virus infection in both ferrets and mice was transient. Epidemiological and clinical experience suggested the same held for humans. Yet in tests with vaccine on ferrets and mice they found that vaccination had two effects: it provided temporary protection from lung infections; and it boosted waning immunity, evidenced by an increase in neutralizing antibodies.[131] It was on this basis that the team tested their vaccine in humans. Preliminary tests with the vaccine were made on a small group of 30 soldiers in 1936. Although there was no epidemic, the team found that one dose 'engendered a very satisfactory rise in antibodies'.[132] Emboldened by this result, the following year they administered the vaccine to 500 military men in different service hospitals, with a similar number of men used as controls. The experiment failed miserably. Scarcely before it began, an epidemic burst upon the soldiers. Vaccination produced no clear signs of antibody, and there was little difference between the unvaccinated and vaccinated, and at least four of the vaccinated developed flu.[133]

The failure of the vaccine highlighted the emergence of what Andrewes called 'a new complicating factor' – antigenic variations among virus strains.[134] Early cross-neutralization tests with the ferrets had convinced the British and American workers that the strains they were isolating in different parts of the world were all of one type. This was interpreted as incontrovertible evidence of flu's virus identity. Yet use of the mouse

neutralization test soon revealed a far more perplexing picture. Francis and Magill first identified antigenic variation with mouse tests in 1936, but neither they nor the NIMR workers attached much importance to it.[135] Their views changed as both groups started to study closely the serology of flu virus and test vaccines.

Antigenic variation, which became the most studied and now best known attribute of flu virus, was elaborated collectively. The British and American workers used cross-neutralization tests, where antiserum from one virus was used to neutralize another virus, to trace what Smith and Andrewes called the 'Serological Races of Influenza Virus'.[136] From the 1937 epidemic, the NIMR workers identified in greater London alone 13 strains with differing degrees of antigenic relation. The addition of 15 other strains identified from other parts of the world made the serological picture even more complex. In New York, Francis and Magill encountered a similar array of variations.[137]

Variations in flu strains illuminated old problems and introduced new ones. Keys to flu's epidemiological puzzles could potentially be found here; so, too, could the changing susceptibility of individuals and populations. Antigenic variation became a 'determining factor' in vaccine production.[138] At the same time, this very factor posed significant challenges for the classification of flu and a massive logistical problem for vaccine production: how to sort out which vaccine to use for a given epidemic. Things only became more complicated when, in 1940, Francis and Magill identified an entirely distinct antigenic type of the virus – now known as influenza B.[139] By then, antigenic variation had become a crucial political and military problem, as the production of a flu vaccine became a pressing concern as British and American governments prepared for war.

The threat of a wartime pandemic propelled efforts to improve serological tools and methods of flu vaccination. With the introduction of the developing chick embryo as the basis for a new serological test and a new system of vaccine production in 1941, mouse neutralization was soon replaced at NIMR and most other laboratories. But as Andrewes presciently noted in 1937, the serological picture elaborated through this test had introduced a 'tangle' that was 'not going to be an easy one to unravel'.[140]

Conclusion

The mouse neutralization test was largely an experimental laboratory tool that virus workers applied to clinical and epidemiological problems. While the MRC and the medical and lay press highlighted the potential value of the NIMR's laboratory techniques to redress longstanding diagnostic problems associated with flu, the serological identification of flu virus in mice did not, at least in the short term, directly change everyday clinical or public health practices. The test was too complicated and too laborious to be used as a routine assay in hospital pathology laboratories. Even when serological tests for flu were eventually simplified they tended to be used for delineating annual flu virus strains and for population-based epidemiological studies. The impact of the mouse test on existing medical knowledge and practice was rather more indirect.

The NIMR workers' efforts to correlate laboratory and clinical work produced a new classification of 'epidemic influenza' as a virus disease. While the integrity of this entity was threatened by the antigenic variation of flu viruses, its potential value in explaining the protean clinical and epidemiological characteristics of flu was not

lost on the medical profession. As early as 1937, medical textbooks had incorporated the virus into explanations of flu's aetiology and used it to elucidate flu's pathogenesis and the nature of its associated immunity.[141] In 1939, the British Ministry of Health made the NIMR workers' viral definition of flu the basis for a new flu memorandum distributed to all public health official in advance of the war. Distinguishing flu from various forms of catarrh and colds was an ongoing problem for physicians and for public health authorities, and the concept of flu as a specific virus disease represented one way to manage clinical knowledge. With diseases like flu, physicians would soon have to learn to differentiate between viral and bacterial infections. This process was hardly straightforward. Flu diagnoses remained symptom-based, with recourse to the laboratory made only in uncertain cases. The persistent conflation of viruses and bacteria through the twentieth century suggests that 'viralizing' medicine faced considerable challenges. Nonetheless, knowing that flu belonged to a category of diseases that eluded modern chemotherapy eventually had bearing on both treatment practices and public health measures. In this respect, flu vaccines would play a crucial role not only in managing the disease but in the incorporation of virus concepts and techniques into everyday medical worlds. The development and routinization of vaccines for polio, chicken pox, measles, and a host of other diseases after the Second World War carved out a place for viruses and virus diseases in modern medicine.

Neutralization tests played a crucial role in giving visibility to virus diseases. In the case of flu, they helped set the stage for its recognition as a major virus disease in the second half of the twentieth century. Although the mouse neutralization test's laboratory life was short, it was not without consequence. The mouse neutralization test was integral to flu's redefinition as a virus disease in the interwar years, and both the ferret laboratory model and the mouse neutralization test raised crucial questions about the nature of flu immunity and how to immunize against epidemics that continued to vex flu research. The genealogy of the problem of the antigenic variation of flu viruses, which became a defining research problem in modern virology, and a constant challenge to health care infrastructures, can be traced back to work done with the mouse test. The uses of the flu virus neutralization test illuminate how the construction of viruses and virus diseases as immunological problems facilitated the translation of esoteric virus work into medical problems, and how these problems were redefined in the process. Virus-neutralizing antibodies were also powerful symbols that, as the medical and lay media highlighted, were suggestive of the ways in which virus research, and virus workers, could control the most challenging of plagues. If, in 1933, virus workers inhabited the periphery of flu medicine, by the Second World War, both they and their animal tools had become indispensable.

Acknowledgements

Notes

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