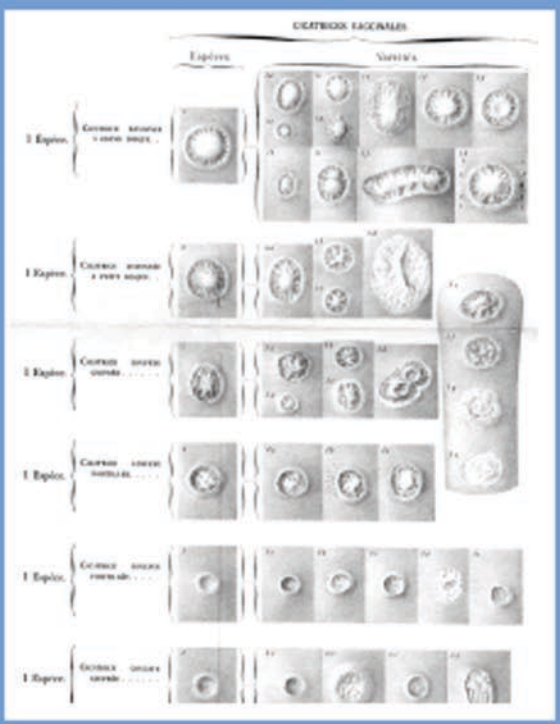
THE HISTORY OF MEDICINE IN CONTEXT

Crafting Immunity

Working Histories of Clinical Immunology



Edited by Kenton Kroker, Jennifer Keelan and Pauline M. H. Mazumdar

CRAFTING IMMUNITY

The History of Medicine in Context

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Crafting Immunity

Working Histories of Clinical Immunology

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CHAPTER ONE

Editors' Introduction

What is Immunity?

This is decidedly *not* the question we initially posed to our colleagues when we first invited them to participate in a conference to be held at the University of Toronto in June of 2004. We had instead issued a call for papers that sought to understand the diverse ways by which immunological knowledge had been articulated in clinical medicine. At that time, not much more than a decade had passed since scholars in science studies began to issue systematic calls for a general reorientation of their field away from the problem of science as theoretical knowledge and towards issues surrounding scientific practice.[1] Historians of immunology were also starting to mine similar territory, eschewing histories that seemed to follow the 'invented traditions' of immunologists themselves and proposing instead that we explore 'histories of vague and contingent subjects such as immunity, infection, or allergy – topics not often identified as part of the patrimonial legacy of the reinvented tradition'.[2] Yet there still seemed to be very little in the historical literature that would help us to find out what immunologists actually did, as opposed to what (or how) they thought. And so we decided to try to fill that lacuna by calling a conference on the link between bench and bedside, as Ilana Löwy has so nicely put it.[3]

The results of our organizational efforts were not quite what we expected. It was not so much the pretences of immunology as a branch of biological knowledge with clinical applications that came under scrutiny as it was the very fact of immunity itself. Throughout the more than two centuries under consideration at the conference, immunity traversed a vast number of domains, from the sweeping claims of public science at the municipal, institutional, national, and even international levels to the micro-practices of histo-pathology, serology, bacteriology, and virology. Immunity served its interlocutors as both idea and experience, as telos and as technique. It could be gendered. It could be standardized. It could even be distributed geographically.

Instead of attempts to historically reconstitute a field of knowledge around practice rather than theory, our conference participants presented us with a series of investigations, each of which showed the way the parameters of immunity had been determined differently in specific contexts. Indeed, in the instances with which our volume begins, it is difficult to identify anything like immunology, properly speaking, even though theories of immunity and their attendant experimental systems did precipitate out of the eighteenth- and nineteenth-century debates over the risks of smallpox vaccination. More recent instantiations of the question of immunity appear no less practical. Identifying and defining AIDS at the National Institutes of Health, for example, seemed to be more a matter of clinical and institutional orientation than

theoretical predisposition, while radioimmunoassays appear to have initially emerged and proliferated less for their theoretical value than for the perceived need to find novel and practical applications of radioisotopes.

In short, our authors had captured the diversity of immunity's history as an investigative object. This volume thus belongs to a larger movement in the sociohistorical study of medicine (and in the study of science more generally) that decentres disciplinary preoccupations in favour of tracing the trajectories of objects, technologies or experimental systems through time.[4] There are, of course, multiple ways of adopting such an approach. Andrew Pickering's idea of the 'mangle of practice', for example, construes practice as a 'dialectic of resistance and accommodation'.[5] He sets off from the catchy slogan of the mangle to present science in terms of scientific realism, as a dialogue between the material world and the actor-network whose negotiations are often invoked by science and technology studies. Each of them, human and nonhuman, is equally important in science. In *Crafting Science*, Joan Fujimura also recognizes that practice involves contingencies and negotiations surrounding the roadblocks or opportunities for participants on the 'shop floor'.[6] Her histories show researchers constructing their problems, defining their area of practice, and negotiating a way forward. Practice here appears as a series of multilateral interactions between actors, events and materials.

Historians of medicine have their own traditions of examining such interactions. Most, if not all, are familiar with the fact that the interaction of clinic and laboratory was the explicit function of the Rockefeller Hospital. Founded in 1910, the Hospital was an objective correlative of the mangle of practice. All who worked there were to be at the same time researcher and clinician. One of those who managed to be both, according to Olga Amsterdamska, was D.D. van Slyke.[7] Van Slyke's work on alveolar CO_2, blood pH and clinical diabetes captured both the clinical laboratory and the clinic in practice: his tests were quantitative and they defined new facets of the disease, even as they answered to the needs of the clinic in being quick and simple enough to allow for close monitoring of a patient. Van Slyke's widely used blood-gas apparatus brought a new instrument to bedside practice. Eighty years on, Alberto Cambrosio, Ronald Guttman and Peter Keating came to a similar conclusion about the use of flow cytometry and its peculiar lymphocyte subsets in the clinic as a means of monitoring graft rejection.[8] The technique had become ubiquitous by 1994, when they published their study. But did the technology drive the clinic, or did the clinic drive technology? That question, they say, is simple but too crude: the diffusion is better described as a pattern of interaction and feedback between an open-ended set of heterogeneous elements, with 'the clinic' and 'technology' as networks of people, tools and practices. Elsewhere, they put that as the 'intersections' between 'human actors, the tools, the entities and the bodies that are constitutive of the new medical technologies'.[9]

Some of these accounts of practice come very close to home: Patricia Gossel's 'A Need for Standard Methods: The Case of American Bacteriology', explains how Robert Koch's tightly controlled and standardized laboratory practices were passed down through his hands-on courses, and could not be mastered by merely reading the literature.[10] In the same collection, Keating, Cambrosio and Michael Mackenzie take on the legendary problem of the definition of avidity and affinity – two words, perhaps with the same meaning, used to express the speed and firmness of antibody binding, which were, and still are, difficult to define in any way other than by practice.[11] The use of such

terms became a touchstone for practitioners in the discipline of immunology: it is only outsiders that need to try to define them, an example of which they provide by examining the course of a patent dispute. A further paper by this extraordinary team deals not with a new machine, but a new style of practice, the clinical trial, hall-mark of the evidence-based medicine of the present day: like the cell-sorter, the protocol has become ubiquitous, and both drives and is driven by the clinic.[12]

Perhaps the richest accounts of immunological practice, however, are the two full-length studies produced by Keating and Cambrosio on the one hand, and by Ilana Löwy on the other.[13] The former's discussion of 'biomedical platforms' frames a compelling argument for the utter transformation of the interplay of the normal and the pathological in a domain that fits rather uncomfortably under the rubric of 'cancer immunology'. The authors work around this term, as their mission is not to describe a theoretically-coherent sub-discipline or field, but rather to show how investigative practice has, since the 1960s, been re-organized with the introduction of a new 'platform' – a term which, like immunity, seems to gain strength from being both ostensible and elusive. One key to this approach is its emphasis on automated systems and their epistemological effects. In comparison to the morphological platform which preceded it (and which is now coextensive with it), flow cytometry acts where humans cannot. Flow cytometry, and biomedical platforms in general, are engineered forms of agency, which redefine and reconstitute surrounding practices, all the way from architectural design to doctor-patient interactions. From the perspective of the platform (on which one is obliged to stand in order to have any perspective at all), the normal and the pathological are no longer separate and distinct spheres of investigation and action. Both are implicated – or rather, built into – the same platform.

Löwy's *Between Bench and Bedside*, on the other hand, derives its power from its ability to reconstruct the perspective of the practitioner and patient. Löwy, the professionally experienced native observer, unlike the naïve anthropologist of some science studies literature, is both historian (who knows the back story even better than the tribe themselves) and watcher from the sidelines. She feels there has been an asymmetry between the basic science of immunology and its clinical applications, at least in the field of cancer treatment. There have been several attempts to use an immunological approach in cancer control over the past century, and this reflects not only theory change but different institutional elements, including the postwar appearance of the new specialized bio-science companies and the development of large, multi-centric coordinated clinical trials. As the system has become larger and heavier, its rhetorical power has increased along with its power as an industrial complex. The centrepiece of her analysis is her 'thick description' of the experimental testing of IL-2, a lymphokine activating a sub-set of cells that, it was hoped, would attack cancer cells. Her account is personal, yet sociological and scientific, so that, as in reading a good novel, you feel you were there yourself, and know the people she knew. The conflicting dispositions, competing interests, shifting grounds and strategic systems of identity, described by Pierre Bourdieu as integral parts of the 'craft' of the scientist, take on flesh and bone in Löwy's account.[14] The system as she saw it demanded close collaboration between the interests involved: the commercial producers of IL-2, the mouse-centred research immunologists, the hospital technicians and clinical staff, and the patients themselves generated a complex series of interactions taking place in the space between biological

knowledge and its clinical application. As she found out, each actor had a personal interest. For some, the results were important as knowledge-gathering, as career-promoting, or as structuring boundaries between immunologists and oncologists. For the patients, the results were not very good: there were some temporary remissions, and some deaths from the effects of treatment, but no true cures. Yet all seem to have shared the doctors' view, itself based on a general, community understanding of the pathology of cancer, that the acceptance of an end-of-life treatment that gave uncertain results and severe side-effects was ultimately a good decision.

So on the one hand, we have a form of engineered stability that draws upon the abilities of the laboratory-based sciences to be simultaneously 'self-vindicating' and innovative.[15] This seemingly paradoxical situation relies heavily on the way that instruments – the focal point of twentieth-century big science – first embody theory, but are then reintegrated into practice only to find novel and unanticipated applications. But on the other hand, we find the dynamics of 'public science', self-identity and belief (not just of practitioners but of patients) presented in a fine-grained sociological analysis of systems of practice that seem particularly attuned to the investigation, regulation and exploitation of biomedical risk.[16] The papers in our volume combine aspects of both approaches. When presented with the challenge of how to get at the historical relationship between the immunology of the clinic and that of the laboratory, many of our participants imagined conflict that played itself out at the level of individuals mounting arguments and claims in an agonistic field. Others depicted the stability achieved through instruments, automated platforms and other regulatory devices. But in each case, there is still to be found here a similar interplay of the normal and the pathological, the theoretical and the practical. There are issues of standards and routines, tools and techniques, concepts and strategies, local knowledge and international agreements, public disputes and private reassurances. Although the clinic figures strongly in each chapter, it is not clear that knowledge of the pathological leads the understanding of the normal in any straightforward way, as Georges Canguilhem suggested many decades ago.[17] After all, when you are mounting claims about smallpox vaccination by correlating morbidity rates to the appearance of vaccination scars, it is uncertain what constitutes 'the normal' of which you are seeking knowledge. It is rather that you are using claims about immunity to usher into existence the very idea of the normal – by persuasion if possible, by legislative force if necessary. It seems rather that, in each of our cases, the question of 'what is immunity'? can be traced back to such interactions. Immunity, not immunology, is the object coming into view, and it does so in each case by virtue of an identifiable, if idiosyncratic, set of practices.

We describe such practice as a craft-like process to reinforce precisely this lack of disciplinary coherence to the diverse ways in which immunity has been constituted as a practical and theoretical object of interest. Our vision of craft is not so much an 'ideal type' as one that can serve to demarcate an epoch of immunology's history distinct from the 'rationalized production' of late-nineteenth-century bacteriological laboratories and the 'systematic innovation' of contemporary immunology.[18] The engineer does not figure strongly in many of our stories. It is rather the case that the investigators under study tend to fashion themselves as engineers of sorts, always attempting to somehow rationalize and thereby disseminate their systems of production, be they of neurotropic viruses or solutions to perennially irritating allergens. Innovation, that much-admired word of university administrators and capital investors, is still on the agenda, though

it more frequently appears here on a local scale. Craftwork is innovative at this level precisely because it involves creative use of the tools available, and is accountable only through analysis of its practical results. Sometimes (as it seems in our studies of allergy and epidemic encephalitis) practitioners' attempt to integrate their results back into immunological theory generate dispute. In other instances, potential instability is silenced by the work of regulatory bodies, be they cyclotrons or international health organizations. Indeed, when taken as a whole, the chapters in this volume present the argument that immunity itself is the product of the craft of negotiating the terrain between the idiosyncratic and individualized ideals of the clinic with the more formalized, regulatory apparatus of the laboratory.

Part I. Reason and Risk

The two chapters in this section describe the invention and rapid adoption of Edward Jenner's smallpox vaccination at the end of the eighteenth century and the coalescence of political, theoretical and practical problems that tempered late-nineteenth century enthusiasm for the practice. Unlike the treatment given in most vaccination histories, our authors reconstruct the rational contexts of eighteenth- and nineteenth-century vaccination practices as integral parts of the experimental systems used to make artificial immunity a visible and reproducible phenomenon. Andrea Rusnock and Jennifer Keelan both describe how convergences in techniques, theory, and instrumentation underpinned the practices and arguments supporting smallpox vaccination.

Rusnock's paper adds a unique perspective to the historiography of early vaccination by adding theoretical dimensions to the familiar story of the invention of vaccination. She argues that Jenner's approach to demonstrating vaccine-immunity was heavily shaped by eighteenth-century natural history and taxonomy. Vaccinia, a pox disease striking cows, was effective in protecting against smallpox because the two diseases were very closely related, if not actually the same, species. Classification was a favourite form of eighteenth-century natural history, in medicine as well as in botany or chemistry. The Edinburgh clinical teacher William Cullen (1710–90), for example, lists at least five recent classification systems, and adds two more from the seventeenth century in his 1783 nosology.[19] His classification of fevers included Variola (smallpox) and Varicella (chickenpox) as genera which were then divided into different species that differed according to severity and other criteria: *Variola discreta* and *Variola confluens*, then, were not the same disease, as they had different symptoms. But they were closely related. Jenner, likewise, could argue that Variola and Vaccinia were close enough to modulate into one another in different hosts. An ontological purist could attack this: they had different hosts, different rashes (the exanthem), and different outcomes. But a drift of one seemingly distinct fever into another was not unknown: the constitution of the year might modulate this year's common fever, acute Synocha, into next year's low nervous Typhus. They did have different symptoms, but they had a family relationship: both of them belonged to Class I, *Pyrexiae*; Order I, *Febres*; Type II, *Continuae*: *Synocha*, *Synochus* and *Typhus*. Ontology on this model was not as sharp-edged as it was later to become a century later with bacteriological specificity, matching species of infecting organism with species of disease as tightly as the Berlin bacteriologists hoped. Clinicians were prepared to see new relationships, intermediate forms and subtle modulations. They

knew how difficult it was to tell one disease from another. As Rusnock demonstrates, it was only after the experiments of rural physicians like Jenner were repeated on tens of thousands of patients in urban smallpox hospitals, that delineation of types could be undertaken and discrete categories of immune responses quantified.

The shift from the naturalist's description of vaccination to a more quantitative and categorical approach created unexpected problems. More data did not result in ever more precise demonstration of immunity, and the theoretical premises that supported vaccination were not easily jettisoned. Keelan shows that, as the nineteenth century progressed, a series of practical and technical problems surrounding the quality of circulating vaccine led physicians and vaccine manufacturers to revisit the theoretical premises of Jenner's experimental system. Vaccination data were difficult to interpret: the disease itself was highly variable and the risks of getting it varied, too. And then there were risks associated with vaccination itself. Technical problems with both vaccine and vaccination remained unsolved. An active anti-vaccination movement led by medical men drew on the same data as the pro-vaccinators, but the two groups came to opposite conclusions: acceptance of the efficacy of vaccination required acceptance of a theory as well as an empirical practice. The attempt to enforce compulsory vaccination in late-nineteenth-century Montreal brought the political element in all this into the open, highlighting the inter-relatedness of the political, theoretical and clinical reasoning involved in government universal vaccination schemes.

Part II. The Conundrum of Allergy

Mark Jackson's paper perfectly fulfilled our editorial hopes that participants would investigate the clinical roots of immunology and its more craft-based aspects. As a group, the allergists never lost touch with their patient-base. As in much early immunological research, the primary object of study in early allergy work was the antidiphtheria serum and its behaviour in clinic and laboratory. The Austrian paediatrician, Clemens von Pirquet, began with a laboratory exercise tracking the curve of the antigen-antibody reaction, but, always a clinician, his analysis of 'serum sickness' (a reaction following the use of the antidiphtheria serum) provided him with a model explanation for the symptoms of childhood infectious disease. Although later workers used Pirquet's word 'allergy', its specific meaning and application was unclear and even controversial. A London group took their cue from Sir Almroth Wright of St Mary's Hospital Vaccination Department, and built up a clinical department that treated allergic patients by immunizing or desensitizing them with the pollens that set off their symptoms, very much as Wright had done with his personal vaccination programme for chronic diseases like acne. Like Wright, they worked closely with a manufacturer, and preferred to rely on a patient's individual feeling of relief or otherwise than upon statistical analyses of signs to support their claims. The patients themselves had considerable influence on their treatment and how it was administered; they were people with a certain class confidence, it seems. Interestingly, as Jackson points out, doctor-patient relationships were fragile and probably did not survive the uniformity of treatment under the National Health Service in 1947.

The nineteenth-century American allergists in Carla Keirns's paper have a different background, but an equally close link with their patients. Like the allergy sufferers of

St Mary's, the patients tended to be upper class, or at least well enough off to go to a more healthful climate in hay-fever season, and to thereby control their own treatment. The US Hay-Fever Association, founded in 1874, was a group of patient-collaborators, some of them doctors, who, like those in a traveller's club, used their members' feedback each year to map out safe destinations. The patients' support society of the early years was replaced after World War I with two regional groups. In the west, the group formed the Society for the Study of Hay Fever, Asthma and Allergy, and in the east, the Society for the Study of Asthma and Allied Conditions; in 1973, they amalgamated to form the American Academy of Allergy. Though these were professional groups, it is noteworthy that some of the leading professionals were also sufferers: as Merrill Chase of the Rockefeller Institute remembered, founder Robert Cooke had asthma attacks triggered by cows and horses, and Arthur Coca suffered from migraine and a number of food allergies.[20] Interestingly, as in St Mary's, the same connexion with commercial drug firms appears: desensitising doses had to be prepared in bulk and marketed. The need to standardize the making of vaccines on a large scale required the help of a commercial laboratory. Coca was to become medical director at Lederle Laboratories, which was marketing sets of allergens for skin testing and desensitizing. Analogies between pollen and bacteria as a model of disease causation kept the allergists attached to main-stream immunology, in spite of their somewhat marginal status.

Part III. Some Tools of the Trade

The two decades that intervened between the first two World Wars has long been recognized by historians as the point at which many scientific fields began to assume their now-characteristic, large-scale organizational structure.[21] Systematic funding from industry and the public purse, widespread media coverage of discoveries, large and even international groups working on projects boasting an extensive integration of support staff, engineers and researchers were beginning to come together, and, more often than not, they converged around a large and expensive instrument. This same period also featured one of the most devastating pandemics since the rise of a new public health grounded in bacteriological research. The chapters in Part III examine the different ways in which British, French and German investigators responded to these developments.

The guiding paradigm of research into immunity, with its central act in the antigen-antibody reaction, or toxin-antitoxin neutralization, was by this time familiar to everyone in the field. Michael Bresalier's paper underlines again the pervasiveness of this view, while at the same time emphasizing the way in which it achieved a more public profile as the key mechanism in the 'device' needed to understand viral epidemics. Virus research at the British Medical Research Council's Hampstead Laboratory was pushed along by the recurring epidemics of flu with their very high mortality that followed World War I. Although the discipline of virology began to appear in the 1930s, its methodology depended largely on the practical lines laid down in the bacteriological laboratory of the last decades of the nineteenth century: it called for a suitable experimental animal, a key tool for any bacteriological project, that would show symptoms of the disease and produce a specific antibody, leading to a neutralisation or a bactericidal effect. The new susceptible animal turned out to be the ferret, through which cultures could be made and experimental transmission of the disease worked out. It seems that laboratory

practice was so well entrenched in standard operating procedures or SOPs that it did not need explicit discussion. Fifty years into its history, bacteriology was strong enough by now to continue with or without bacteria. But this could not have happened without the concept of immunity, which, through its employ by the MRC as a modernizing device that translated laboratory practices into clinical effects, definitively established flu as a viral disease in the public mind.

Immunity was fast becoming visible in other ways, and Kenton Kroker's study unveils how laboratory investigations into the cause of a deeply symbolic viral disease were depicted at the Pasteur Institute during the 1920s. Viruses were then defined as invisible entities, as they passed through porcelain filters which embodied the very limits of light microscopes at the time. But, given the rhetorical power of the 'immunological devices' described by Bresalier, other visual strategies lent themselves to the imagination of Constantin Levaditi, to powerful ontological effect. Levaditi's work on epidemic encephalitis, a neurological disease with an extremely loose and ill-defined collection of symptoms, made a virtue out of necessity. Viruses could only be identified by a combination of their behaviour as filter-passers and through their effects, which included a specific histo-pathology, and a specific immunity. So Levaditi crafted a complete visual, iconographic system that depicted and defined a group of neurotropic viruses as a function of time and tissue, rather than morphological space. Where others, such as Simon Flexner of the Rockefeller Institute, had failed in their efforts to capture the virus of epidemic encephalitis, Levaditi had used immunity and its cellular effects to change the very rules of the game of capturing viruses, in time, or in space.

Anyone examining the history of the Pasteur Institute will find plenty of connexions between laboratory and clinic. In fact, the Institute between the wars was a scene so clinic-based that it was once labelled 'low-grade artisanal practice', a sign of the relative backwardness of French medicine, waiting for the cleansing effect of the afflux of US-based biomedicine that came after World War II.[22] New, more scientific methods swept away the colloidal point of view that had characterized the thought of *pasteuriens*, along with the old French vitalistic emphasis on the clinic rather than the laboratory. But, as Löwy argues in her chapter, colloid chemistry as the chemistry of life forms is *both* reductionist (as physical chemistry) *and* holistic or vitalistic (as an explanation of clinically manifested disturbances of the body). And in France, in particular, this particular form of conceptualizing immunity in terms of colloids, cellular reactions, and anaphylactic effects, characterized here as the 'anaphylactic episode' in French medicine, effectively bridged the very public innovations of the Pasteur Institute with the more majestic heritage of the clinical tradition. While the tendency has been to deride this episode as the last gasp of holism in the face of the triumph of reductionist biomedicine, Löwy cautions against such simplistic dualisms. She instead argues that this period reveals the enormous difficulties in transplanting immunological knowledge into the clinical domain, suggesting, perhaps, that if we look closely, the divide between the clinical practice of the 1930s and the early twenty-first century becomes more apparent than real.

The uncanny ability of *pasteuriens* to philosophize by other means finds its limits in Pauline Mazumdar's story of the standardization of serotherapy. No less than cherished holistic precepts, vaccines and their assays were dependent on the cellular tradition of the Pasteur Institute, and on the choice of colloidal precipitation rather than bio-assay

as a standardization system. Paris's cells, colloids and vaccines, as Mazumdar brings out in her contribution, formed a disputed frontier with those trained in the German tradition of serological standardizing by the Frankfurt toxin neutralization method of bio-assay with its many guinea pigs. This was more than a mere technical problem of the standardization of dosage for the serotherapy of diphtheria or tetanus: with the recent conclusion of hostilities and an aspiring international governing body, political elements were also at work. But it seems that the Pasteur Institute's 'artisanal' vaccine producers had a longer future ahead of them than the laboratory-based serologists of the League of Nations Standardisation Commission. In practice, prevention trumped cure, and craft defied regulation. The standardization of substances designed to create immunity in diphtheria, tetanus and dysentery ultimately followed very different trajectories.

Part IV. Insiders, Immunity, and Identity after World War II

The final part of our collection begins with Angela Creager's paper on radioimmunoassay. Her story dates to the end of World War II, when excess military production of radio-isotopes was promoted for use in civilian society, beginning in the 'insider' military hospitals of the Veteran's Administration. The technique was one of the outgrowths of the *in vitro* colloidal precipitation tests of the twenties and thirties, such as the Kahn test for syphilis.[23] The new version, where one of the components of the antigen-antibody reaction was labelled with a radioisotope or in some cases with a fluorescent dye, was more sensitive, and more quantitative, than the old guesstimates of flocculation in tubes held up to the light. Its first clinical success came with the detection of anti-insulin antibodies in diabetics: the antibodies were directed at the foreign insulin, not to their own pancreatic product. The situation mirrored the development of serum sickness in patients who had been given horse antidiphtheria serum in the first decades of the century. By 1975, notes Creager, more than 4,000 hospital diagnostic laboratories were using radioimmunoassays. In the 1980s, commercially available kits took advantage of the new monoclonal antibodies whose 'exquisite specificity', in Cambrosio and Keating's phrase, still further enhanced the sensitivity of the method.[24] We now rely upon radioimmunoassay for diagnostic tests to detect a long list of substances of clinical importance; it is ironic that the methodology was built upon the colloid precipitation tests that were regarded as so subversive in the interwar period.

With our next essay, we let go of the simple serological antigen-antibody reaction, and enter the period of the dictatorship of the lymphocyte, as the Soviet immunologist Rem Petrov called it.[25] Like the phenomena of allergy and anaphylaxis, pregnancy has long presented a challenge to the essential antagonism between self and nonself presupposed by most immunological theory. This model conformed well to the experience it was originally devised to explain; namely, falling ill from infectious disease. Yet such a model all but precluded an immunological analysis of reproduction, an activity of considerable importance to the species. In fact, the question of the nature of maternal immunity during pregnancy seems to have eluded immunology's founding fathers entirely, even as they worked around problems of reproduction: Ehrlich, for example, made an immunological analysis of mother's milk while Metchnikoff focused on invertebrates and the ontogeny of immune cells.

During the 1950s, the graft or transplant, with its foreign histocompatibility antigens activating the cellular defences of the recipient, came into its own as an explanatory device. Even as he cautioned against exaggerating the usefulness of pathologies in pregnancy for understanding immunological intolerance in the early 1950s, Peter Medawar usually cast the foetus as a graft or transplant, raising maternal reactions generally seen as defensive.[26] During the 1960s and early '70s, the foetus and mother became indelibly stamped as foreign organ and host, or, as two of Medawar's colleagues baldly stated, 'Nature's carefully coordinated preparation of her grafts and the "beds" intended to receive them'.[27]

Moira Howes, a feminist philosopher, takes on this ideologically loaded problem. Is the foetus a foreign body within the mother, or is it her own body – a body part, in fact? In this case, she feels the self/not-self paradigm of graft rejection has constrained research by subconsciously guiding experimental practice in the clinical field of the investigation of infertility. She proposes a new model: the foetus is neither a transplant nor a body part, but something in between. She posits a less sharply-defined immune self, using pregnancy as its model relationship, rather than relegating pregnancy to the realm of the pathological exception which has to be explained, somehow. 'Pregnancy', she says, 'points to selfhood as it really is, nebulous, but self-sufficient'. It is possible for a model to persist in laboratory practice even when it has been questioned or even discredited. Polly Matzinger suggests that instead of self/non-self, we might try the 'danger signal', which is close to Barbara Katz Rothman's body-part model.[28] If the foetus emits no danger signal, the mother's immune system is not activated; attention is focussed on protection and maintenance, as it would be if the foetus actually were a body part. This seems better, but it is still not enough, argues Howes, to account for the positive protective effect of the mother's immunological involvement in the pregnancy.

The advent of fertility clinics in the last decades of the past century changed the situation very little. As Howes observes, even those theoretical assumptions that have been nominally overturned can become embedded in practice. Despite the resolute focus on 'women's health' that must obviously be maintained by such clinics, they nonetheless persisted in characterizing maternal contributions to immunological function during pregnancy as pathological or passive

As the resident or embedded historian of the US National Institutes of Health, Victoria Harden offers an insider's access to some unique sources, collections and contacts. Her interviews with the makers of AIDS research in the eighties have an intimacy that makes her more like a primary source: she was actually *there* at the time. In her paper, the lymphocyte is no longer a dictator: by 1984, it had become the helpless victim of the AIDS virus.

By the early eighties, when AIDS appeared on the scene, new tools were available to immunologists. Monoclonal antibodies had enabled the seemingly identical swarm of lymphocytes to be divided again and again, into several different antigenic families, many with well-defined functions, co-ordinated by the lymphokines. New instruments based on flow cytometry used antibody tagged with fluorescent dyes to activate cell counters; antigenically distinct cells were now easier to distinguish, and many new antigenic subgroups were defined. In 1975, the Fluorescence Activated Cell Sorter came on the market, allowing the operator to collect segregated populations of different cells. As Keating and Cambrosio have detailed at length, though both fluorescence tagging

and automated particle counting dated back to the sixties, the new machines utilizing the sharper specificity provided by monoclonal antibodies took differentiation between cells to a different level, and provided a new platform from which to work.[29] The cell populations were created, as it were, by the machines, which then became the key to AIDS investigations, both for research and for clinical assessment of patients. Instead of the immunologists struggling to grasp the fact of different populations of lymphocytes (as one of us well remembers from 1968), the man-in-the street could now be heard enquiring about the health of a friend's CD4 count. In 1981, the National Institutes of Health's National Cancer Institute (NCI) acquired a cell sorter. AIDS, explains Harden, did not fit neatly into the NIH structure. It just happened that the National Cancer Institute had the money to pursue this particular avenue of research.

The practical significance of low cell counts produced by the machines is evident in the terrible case histories of multiply-infected patients: one man had Pneumocystis carinii pneumonia, cytomegalovirus, Herpes simplex, candidiasis, and Mycobacterium avium tuberculosis. He could neither make immune globulin nor respond to a tuberculin skin test, even though he had tuberculosis. But a pilot study by the NCI found that CD4 and CD8 cells were often low even in asymptomatic patients, if they were gay. The unknown infectious agent that triggered all this had to be something that attacked T-lymphocytes. As in Levaditi's research on Encepalitis lethargica, and the flu virus research of the thirties, the cause was invisible, but the effects were profound.

Harden feels that the understanding of the T-cell defect depended wholly on the growth of molecular immunology. In terms of the intracellular pathway of the retrovirus, that is clearly true. But, as Richard Krause, the Director of the National Institute of Allergy and Infectious Disease from 1975–84, is quoted by Harden as saying:

> The principles for identifying sexual transmission of a disease were in place … We would have used cruder immunological techniques to make a diagnosis. A 1950s serological test would have been more primitive, but I think we would have come up with something …

In contrast, Anthony Fauci, Director since 1984, emphasized to Harden how molecular thinking had made older models of disease seem helpless: 'I think we would not have had a clue', he concludes.

Christopher Rutty's essay is based on archives that are generally inaccessible. Like Harden, he is an embedded historian in his institution, and they share a similar kind of intimacy with their material. As he says, it is very unusual for anyone to be given access to a manufacturer's archives, if in fact any archival material has actually been kept. Rutty deals with the practical issues of smallpox vaccine production between 1917 and 1980, testifying to the legacy of the technical problems that had bedevilled Keelan's Montreal vaccinators twenty years earlier. The continuity of problems is unmistakable. He writes of the day to day concerns: the bulk production of consistently efficacious vaccine, the sterility problem, the packaging, and the need to conform to all possible standards – Canadian, American and those of the World Health Organization as it struggled with its smallpox eradication campaign.

* * * * *

These papers share a point of view: the history they reveal is a working history. Immunity has an active presence in many different fields, and involves clinicians, patients, instruments, techniques, and manufacturers negotiating with each other and with the laboratory. Theories and paradigms are a questioning presence in the background, but the real action appears to be elsewhere.

Notes

1 See, for example, the essays in Andrew Pickering (ed.), *Science as Practice and Culture*, Chicago: University of Chicago Press, 1992.

2 Warwick Anderson, Myles Jackson and Barbara Gutmann Rosenkrantz, 'Toward an Unnatural History of Immunology', *Journal of the History of Biology*, **27**, 1994, pp. 575–94, at p. 576.

3 Ilana Löwy, *Between Bench and Bedside: Science, Healing and Interleukin-2 in a Cancer Ward*, Cambridge, Mass.: Harvard University Press, 1996.

4 See, for example, Lorraine Daston (ed.), *Biographies of Scientific Objects*, Chicago: University of Chicago Press, 2000.

5 Andrew Pickering, *The Mangle of Practice: Time, Agency and Science*, Chicago: University of Chicago Press, 1995, at p. xi & 11; see also idem, 'Objectivity and the mangle of practice', *Annals of Scholarship*, **8**, 1991, pp. 409–25.

6 Joan H. Fujimura, *Crafting Science: a Sociohistory of the Quest for the Genetics of Cancer*, Cambridge, Mass.: Harvard University Press, 1996, pp. 155–83.

7 Olga Amsterdamska, 'Chemistry in the Clinic: The Research Career of Donald Dexter van Slyke', in Soraya de Chadarevian and Harmke Kamminga (eds), *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s*, Amsterdam: Harwood, 1998, pp. 47–82.

8 Peter Keating, Alberto Cambrosio and Ronald Guttman, 'New Medical Technologies and Clinical Practice: A Survey of Lymphocyte Subset Monitoring', *Clinical Transplantation*, **8**, 1994, pp. 532–40

9 Margaret Lock, Allan Young and Alberto Cambrosio (eds), *Living and Working with the New Medical Technologies: Intersections of Inquiry*, Cambridge: Cambridge University Press, 2000, p. 1.

10 Patricia Peck Gossel, 'A Need for Standardised Methods: The Case of American Bacteriology', in Adele E. Clarke and Joan H. Fujimura (eds), *The Right Tools for the Job: at Work in Twentieth Century Life Sciences*, Princeton, NJ: Princeton University Press, 1992, pp. 287–311.

11 Peter Keating, Alberto Cambrosio and Michael Mackenzie, 'The Tools of the Discipline: Standards, Models and Measures in the Affinity/Avidity Controversy in Immunology', in Clarke and Fujimura (eds), *The Right Tools for the Job* (n. 10), pp. 312–54.

12 Peter Keating, Camille Limoges and Alberto Cambrosio, 'The Automated Laboratory: The Generation and Replication of Work in Molecular Genetics', in Michael Fortun and Everett Mendelsohn (eds), *Practices of Human Genetics*, Dordrecht and Boston: Kluwer Academic Publishers, 1999.

13 Peter Keating and Alberto Cambrosio, *Biomedical Platforms: Realigning the Normal and the Pathological in Late-Twentieth-Century Medicine*, Cambridge, Mass.: MIT Press, 2003; Löwy, *Between Bench and Bedside* (n. 3).

14 Pierre Bourdieu, *Science of Science and Reflexivity*, Chicago: University of Chicago Press, pp. 32–85.

15 Ian Hacking, 'The Self-Vindication of the Laboratory Sciences' in Pickering (ed.), *Science as Practice and Culture* (n. 1), pp. 29–64.

16 For a classic analysis, see Steve Epstein, *Impure Science: AIDS, Activism, and the Politics of Knowledge*, Berkeley and Los Angeles: University of California Press, 1996.

17 Georges Canguilhem, *The Normal and the Pathological*, trans. Carolyn R. Fawcett, New York: Zone Books, 1991.

18 These categories are borrowed from John V. Pickstone, *Ways of Knowing: A New History of Science, Technology and Medicine*, Chicago: University of Chicago Press, 2000.

19 William Cullen, *Nosologiae Methodicae, sistens Morborum Classes, Genera et Species, cum harum Sauvagesio Synonomis*, Philadephia, PA: Hodges, 1783, p. 138.

20 Merrill W. Chase, 'Irreverent recollections from Cooke and Coca, 1928–1978', *Journal of Allergy and Clinical Immunology*, **64**, 1974, pp. 306–20.

21 For examples, see Pnina Abir-Am, 'The Discourses of Physical Power and Biological Knowledges in the 1930s: A Reappraisal of the Rockefeller Foundation's Policy in Molecular Biology', *Social Studies of Science*, **12**, 1984, pp. 225–63; Robert E. Kohler, *Partners in Science: Foundations and Natural Scientists, 1900–1945*, Chicago: University of Chicago Press, 1991; Lily E. Kay, 'Laboratory Technology and Biological Knowledge: The Tiselius Electrophoresis Apparatus, 1930–1945', *History and Philosophy of the Life Sciences*, **10**, 1988, pp. 51–72.

22 Jean-Paul Gaudillière, *Inventer la biomedicine: la France, l'Amérique et la production des saviors du vivant*, Paris: La Découverte, 2002.

23 Pauline M.H. Mazumdar, '"In the Silence of the Laboratory": The League of Nations Standardizes Syphilis Tests', *Social History of Medicine*, **16**, 2003, pp. 437–59.

24 Alberto Cambrosio and Peter Keating, *Exquisite Specificity: The Monoclonal Antibody Revolution*, New York, NY: Oxford University Press, 1995.

25 Rem V. Petrov, *Me or Not-Me: Immunological Mobiles*, Moscow: Mir Publishers, 1987.

26 Peter Medawar, 'Some immunological and endocrinological problems raised by the evolution of viviparity in vertebrates', *Symposia: Society for Experimental Biology*, **44**, 1953, pp. 320–38.

27 Alan E. Beer and R.E. Billingham, 'Immunobiology of Mammalian Reproduction', *Advances in Immunology*, **14**, 1971, pp. 1–84, at p. 3.

28 Barbara Katz Rothman, *Recreating Motherhood: Ideology and Technology in a Patriarchal Society*, New York, NY: Norton, 1989.

29 Keating and Cambrosio, *Biomedical Platforms* (n. 13), pp. 123–54.

PART I
Reason and Risk

CHAPTER TWO

Making Sense of Vaccination *c.* 1800

Andrea Rusnock

At the beginning of the twenty-first century, the triumph of vaccination seems self-evident and secure. Vaccination is responsible for the elimination of naturally occurring smallpox. Its principle has been adapted to the control of many other diseases and has contributed significantly to the development of the field of immunology. Two hundred years ago, the success of vaccination, of course, was not at all certain. In 1798, when Edward Jenner published *An Inquiry into the Causes and Effects of the Variolae Vaccinae*, his contemporaries struggled to make sense of his discovery and his success depended on his ability to convince other physicians to adopt vaccination.

For historians, this process of understanding, of making sense of Jenner's *Inquiry*, means placing vaccination within the medical practices and theories of the time and showing how these framed the early evaluation and interpretation of Jenner's results. With respect to practice, most of the physicians interested in testing the efficacy of Jenner's vaccine and its reported advantages over inoculation turned to the hospitals and clinics that opened in the last half of the eighteenth century. These relatively new institutions provided opportunities to conduct systematic trials. In terms of theory, Jenner and his contemporaries approached vaccination through natural history, not immunology, a field that did not develop until the late nineteenth century. Jenner wanted the readers of his *Inquiry* and prospective vaccinators to focus on the classification and description of cowpox and its relation to smallpox. These were the arguments Jenner used to make sense of vaccination, and they are the focus of this essay.

Practice

The basic outlines of the story of Jenner and vaccination are well known. Early in his career as a country practitioner, Jenner noted that individuals who had suffered a bout of cowpox seemed to be safe from smallpox. In 1796, he deliberately infected a boy, James Phipps, with cowpox taken from an infected milkmaid, and then later inoculated Phipps with smallpox to no effect. Jenner wrote up the trial and sent the announcement of his discovery to the Royal Society, who politely declined to publish it for lack of evidence. Jenner then diligently compiled 23 case histories, added an introduction discussing the origins of cowpox, and privately published his *Inquiry*, thus launching a revolution in medicine.

Jenner, as historians are wont to point out, was not so much the discoverer of vaccination as the person most responsible for introducing the technique.[1] Others, such as the Dorset farmer Benjamin Jesty, had tried inoculating cowpox against smallpox, but they had not substantially changed medical practice. The reason was straightforward:

through much of the eighteenth century there already existed a very successful medical technique for providing immunity to smallpox, namely, inoculation. The introduction of vaccination was thus a process of replacing an already accepted technique with an unproved one. Inoculation versus vaccination: this was the debate, and winning this debate was Jenner's objective.

In the 1790s, it was generally accepted that inoculation worked and it was widely practiced among the general population. In the 1720s, the decade during which inoculation was introduced in England, an extended controversy over the morality and mortality of the practice had been resolved in favor of inoculation. This context is crucial in several respects. First, the basic idea behind inoculation was accepted: a healthy individual was deliberately infected to provoke a usually mild case of smallpox, which exempted that individual from a subsequent attack of more virulent natural smallpox. Second, the method of inoculating by taking pox matter and inserting it in the skin, had become routine. Third, the widespread adoption of inoculation encouraged some individuals, most notably the physician and Fellow of the Royal Society John Haygarth, to envision a world without smallpox.[2] That is, the successful practice of inoculation informed contemporary views about humans' ability to control and prevent disease. By 1800, inoculation had contributed to a significant shift in mentality regarding the scope of preventive medicine.

Equally important, inoculation framed the early reception of vaccination in terms of *how* it would be evaluated. Participants in the early debates about inoculation had introduced two new methods to evaluate its safety and efficacy:

1. Observation of individual cases including deliberate human experimentation
2. Statistical comparison of inoculated and non-inoculated populations

The most famous example of the first method was the experiment conducted under the patronage of the Princess of Wales. In 1721, six prisoners from Newgate prison in London were inoculated. All but one prisoner recovered from a mild case of smallpox, and the exception, who was later discovered to have already had smallpox, had no reaction at all. All were set free.[3] The second method was developed by James Jurin, physician and secretary to the Royal Society, during the 1720s. Jurin's numerical comparison of the mortality of inoculated and natural smallpox stands as the first example of medical statistics.[4] Taken together, these new evaluative methods convinced some physicians, natural philosophers, and the public that inoculation worked.

In their early evaluations of vaccination, Jenner and his contemporaries pursued the same methods. In his *Inquiry,* Jenner followed the first method through his presentation of 23 case histories of patients who either contracted the cowpox naturally or who were deliberately vaccinated with cowpox. These case histories were drawn from several years' practice in different locations. Many patients were subsequently exposed to natural smallpox or inoculated with smallpox. It is important to stress that Jenner's contemporaries did not consider the inoculation of an already vaccinated individual as unethical. On the contrary, inoculation was the *accepted* practice. There were no ethical barriers to testing the efficacy of vaccination by observing whether the vaccinated patient reacted to smallpox inoculation.

Jenner's use of case histories to prove the efficacy and safety of vaccination drew upon an established tradition within medicine and spoke to the importance of practice to the creation of new medical knowledge. Information about inoculation and vaccination was collected at patients' bedsides, not at laboratory benches. Case histories allowed physicians to note the specific nuances and idiosyncrasies of each patient and, at the same time, describe and characterize the typical course of a disease and its usual treatments.

Jenner was not a statistical thinker. Although he numbered his case histories, he did not tabulate or quantify the results of his cases. Instead, he compiled one case history after another. The effect was cumulative, not additive. He noted the peculiar characteristics or features of specific cases and discussed how these features might aid in the general understanding of vaccination. So, for example, Case IX, William Smith, illustrated for Jenner the possibility that an individual could contract cowpox more than once, a fact that made cowpox different from smallpox.[5]

Some early reviewers of Jenner's pamphlet were uncomfortable with the quantity of evidence he presented. George Pearson, physician to St George's Hospital in London and a chemist who translated Antoine Lavoisier's *Nomenclature Chimique*, was one of the first London physicians to try Jenner's vaccination. Nonetheless, Pearson charged that 'the testimony of a single observer, however experienced, and worthy to be credited … is insufficient for procuring such facts a general acceptance'.[6] In order to boost Jenner's credibility, Pearson supposed that Jenner's published case histories were 'selected for illustration', and that 'several hundred instances must have fallen under his own observation'.[7] After thus reassuring himself, Pearson devoted the remainder of his pamphlet to evidence in support of vaccination from his own practice and from correspondence with other physicians. For Pearson, large numbers of trials made by several physicians were necessary for demonstration.

Jenner's use of case histories was in part a product of his country practice. He attended individual patients in their homes. Pearson and other early vaccinators worked in cities. They carried out their trials in hospitals or clinics. Indeed, hospitals were a key medical innovation in the late eighteenth century, and increasingly, physicians gained their reputations through hospital appointments.[8] The origins of hospital medicine have been traditionally located in Paris during the French Revolution.[9] Recently, the historian Othmar Keel has done careful studies to show how this picture needs substantial revision. His work shows that hospital medicine emerged in many European countries, including Great Britain, during the second half of the eighteenth century due to a variety of socio-political and institutional factors, including demographic changes, increased state involvement in public health, and humanitarianism. The new hospital medicine helped to merge surgery and medicine, to create new understandings of disease based on pathological anatomy rather than humoral imbalance, and to medicalize institutions of social control.[10]

Most scholarship on hospital medicine has focused on the development of pathological anatomy, but hospitals also functioned as places to evaluate medical practices. The Swiss physician-historian Ulrich Tröhler, for example, has discussed the evaluation of various preventives and therapies at British military hospitals during the second half of the eighteenth century. Tröhler places his analysis within the context of the history of medical statistics and evidence-based medicine, and he explains how empirical evaluation became acceptable within mainstream medicine. 'Bacon's

distinction between "ordinary experience" and "ordered experience"', Tröhler concludes, 'started to be applied in medicine' in the late eighteenth century.[11]

Similarly, Andreas-Holger Maehle has explored the more ordered approach to therapeutics that began to emerge both inside and outside of hospitals in the eighteenth century. In his study of lithrontroptics, opium, and Peruvian bark, Maehle shows that the 'case history approach' predominated. Reports of individual cases were published to evaluate the effects and benefits of various medicines:

> There was a conscious tendency in the course of the eighteenth century to increase the numbers of case reports concerning a particular therapeutic issue, such as Mrs Stephens's medicines against bladder stones or Peruvian bark in "gangrene", in order to obtain more reliable overall results. Towards the end of the century, the numbers and ratios of "cures", relapses, or deaths after different treatments were sometimes retrospectively compared with each other … In this way the occasional trying out of medicines in individual patients was gradually transformed into actual therapeutic trials.[12]

The evaluation of smallpox vaccination partook of both old and new approaches. Jenner collected case histories and compiled them into his *Inquiry.* His supporters evaluated vaccination in London, Paris, Vienna, and Boston hospitals, the new places for trials or ordered experiences. These hospital trials were initially small in size, typically including fewer than twenty persons and were the same in procedure. Individuals were vaccinated, and were then inoculated with smallpox to test the vaccine's success, which was defined as immunity against smallpox. If the patient did not react to the inoculation or had only a mild reaction, the vaccination was deemed successful.

In England, among the first physicians to test Jenner's vaccine was William Woodville, author of an extensive history of inoculation in Great Britain and director of the London Smallpox and Inoculation Hospitals, established in 1747. In January 1799, Woodville vaccinated six patients at the Smallpox Hospital with lymph taken from an infected cow housed in a dairy in Gray's Inn Lane. He kept detailed records of the symptoms exhibited by each patient. After this small clinical trial, Woodville carried out over 500 vaccinations on patients at the London Smallpox Hospital. Many of these individuals were also later inoculated with smallpox to no effect, a demonstration of their immunity to smallpox. Woodville published the results in May 1799.[13]

In Austria, Johann Peter Frank conducted a public vaccination trial at his clinic in Vienna on 1 September 1801. Thirteen children were vaccinated with cowpox; they were subsequently inoculated with smallpox with no reaction. Following this trial, vaccination was officially recommended.[14] In Boston, under the supervision of the physician Benjamin Waterhouse, 19 boys were vaccinated in August 1802 at a newly built hospital on Noddles Island near the Long Wharf. In November, the boys were inoculated with no reaction. Two unvaccinated boys were inoculated at the same time and both came down with smallpox, thus demonstrating that the inoculated matter was active. A broadside was published announcing the success of Waterhouse's trial.[15]

Much broader trials were conducted in France. The Comité Central de Vaccine, established in 1800, was granted permission by Lucien Bonaparte, Minister of the Interior, to test vaccination on foundlings. An initial trial occurred at the Hôpital de la Pitié in June 1800. The vaccine, however, produced bad reactions and the trial was discontinued. Woodville then traveled to France with a fresh supply of cowpox.

A vaccination hospital was set up near the Hôtel de Ville and numerous vaccinations were performed. These trials were more successful and were carefully detailed in the Committee report published in 1803. This report endorsed vaccination and free vaccination clinics were soon established throughout France. [16]

As these examples illustrate, the emergence of hospital medicine strongly shaped the early assessments of vaccination. Certainly the extensive trials conducted on foundlings in Paris would have been impossible outside a clinical setting. In addition to housing many patients, hospitals facilitated the collection of medical statistics.[17] Numerical evaluations of vaccination took place in the first years of the nineteenth century. In response to a smallpox epidemic in 1806, King George III and Parliament asked the Royal College of Surgeons their opinion on vaccination. The College had compiled statistics for 164,381 vaccinations. Only fifty-six patients had contracted smallpox, and just three had died.[18] Likewise, the Comité Central de Vaccine collected information on the number of vaccinations performed throughout France and their results. These data were analysed by the mathematician and economist E.E. DuVillard who published a pamphlet in 1806 that examined smallpox mortality and the potential effects of vaccination on population and longevity.[19] His analysis showed the devastating impact of smallpox mortality and the considerable benefits brought by vaccination.

All of these ways to make sense of vaccination were emphatically empirical – that is, inoculation and vaccination were legitimated through successful practice. Trials, carried out in the countryside or the urban hospital, coupled with quantitative analyses of large numbers of cases furnished proof that vaccination was safe and effective. Thus Jenner and his contemporaries found means to measure immunity and to demonstrate that vaccination worked. But *why* did it work?

Theory

The historian and physician Anne Marie Moulin has examined what she calls 'the paradox of immunization without immunology'. Inoculation, vaccination, and Pasteur's rabies vaccine were all developed without any 'theoretical advances in the understanding of immunity'.[20] The immunologist and historian Arthur Silverstein also points to 'the surprising absence of any hint of speculation in Jenner's writing on what he thought was the mechanism of vaccination in providing immunity to smallpox'.[21] And many textbook histories of immunology state that theories of immunity developed only after the emergence of germ theory in the late nineteenth century. In general, empirical demonstrations of the efficacy of vaccines took precedence over theoretical accounts of how they worked in the eighteenth and early nineteenth centuries.

As Moulin and Silverstein have shown, the idea of acquired immunity existed before the emergence of immunology as a field. The term immunity comes from the Latin *immunitas,* which referred to a legal exemption from service.[22] It was sporadically applied to disease beginning in the Middle Ages and became widely used as vaccination was adopted in the early nineteenth century. Quite literally, immunity in the early nineteenth century meant exemption from smallpox. The question to be explained was how did one become exempt?

Explaining *why* inoculation worked was in one sense quite straightforward. It was common knowledge that individuals who had recovered from a natural case of smallpox

were exempt from future attacks. This was so widely accepted that few undertook to explain the fact. Instead, writers addressed the question of whether inoculated smallpox was simply a milder version of natural smallpox. If inoculated and natural smallpox were the same disease, then there was no question of the practice producing immunity. Thus, Thomas Nettleton, one of the first inoculators to practice outside of London, wrote in 1722:

> In short, as this Distemper [inoculated smallpox] is raised by an Ingraftment from the Small Pox, as it has the very same Appearance, and as it is capable of producing the same by Infection, there seems to be no room to doubt of its being the true and genuine Small Pox. And if that be allowed, it will follow from thence, as a Corollary, that *Those, who have been inoculated, are in no more Danger of receiving the Distemper again, than Those who have had it in the ordinary Way.*[23]

In an earlier letter, Nettleton had observed that 'we have not yet found, that ever any had the Distemper twice; neither is there any Reason to suppose it possible, there being no difference that can be observed betwixt the Natural and Artificial Sort, (if we may be allow'd to call them so) but only that in the latter the Pustules are commonly fewer in Number, and all the rest of the Symptoms are in the same proportion favourable'.[24]

Providing a reason for why inoculated smallpox was milder than natural smallpox was more difficult. One attempt came not from a physician, but from a Boston minister, Cotton Mather, who was an early and fervent supporter of inoculation. Mather argued that the method of infection was of critical importance. Inhaling smallpox miasma brought it immediately to the lungs and heart, while inoculation through the skin only affected the periphery of the body. This could explain the difference in the severity of the two types of smallpox. But Mather was careful to remark that inoculated smallpox nonetheless entered the body in sufficient force to make it invulnerable to future infection. The inoculated smallpox takes, consumes, or devours whatever makes the body susceptible to natural smallpox. 'The Enemy, 'tis true, gets in so far, as to make some *Spoil*', Mather explained, 'even so much as to satisfy him, and leave no *prey* in the Body of the Patient, for him ever afterwards to seize upon'.[25] Mather's explanation has been referred to as the depletion theory of immunity.[26]

The case for how inoculation produced acquired immunity, then, hinged on the idea that inoculated and natural smallpox were the same disease and that once seized with either type, the human body would be forever exempt from future attacks. Vaccination, it would seem, provided a formidable challenge to this explanation for acquired immunity. How could cowpox provide safety against smallpox? Were they variations of the same disease or distinct diseases?

This issue came at a time when the very idea of disease was in flux. By the end of the eighteenth century, physiological views of disease as an imbalance within the body had largely been displaced by ideas about contagion and disease specificity. Inoculation had helped strengthen these new concepts of disease, as had the eighteenth-century preoccupation with classification in general, epitomized in Linnaeus' new system of plant classification. Borrowing from Linnaeus, physicians such as William Cullen and François Boissier de Sauvages created influential nosologies: hierarchically arranged taxonomies of diseases based on their symptoms.[27] Each disease was considered a

distinct species. In Cullen's system, for example, smallpox appeared in the First Class of Diseases (Pyrexia), Order 3 (Exanthemata), and Genus 28 (Variola). Genus 29 was 'Varicella' or chickenpox. Cullen distinguished two species of Variola, 'Variola discreta' and 'Variola confluens', based on the appearance of the pocks and the duration of the fever. Cullen thus sought to record and order distinct disease species based on their symptomology.[28]

Jenner worked within this nosological framework, and one of his goals was to show how cowpox and smallpox were varieties of the same disease. Jenner's approach to natural history, however, was somewhat different than Cullen's.[29] Instead of focusing solely on disease symptoms, Jenner examined a much broader range of characteristics, including where the disease could be found, who was most likely to contract it, and how the disease might change, depending on its environment. This tradition of natural history co-existed with the more narrowly defined classificatory enterprises represented by Linnaeus and Cullen.[30] Jenner's rural practice in Gloucestershire strongly shaped his approach to disease.

In his *Inquiry*, Jenner speculated that smallpox and cowpox were modified forms of horsepox, or what he called grease.[31] In evidence, he noted the incidence of cowpox depended on the gendered division of farm labor. 'If the Cowpox be unknown in the Country in which you dwell', Jenner wrote to Jean de Carro, a Genevan physician who later became one of the leading vaccinators outside of England,

> I should presume that Men Servants, who are employ'd among Horses, are not employ'd in milking Cows. In Ireland, & in Scotland, where the Men Servants do no milk, the disease is also unknown.[32]

Cowpox only flourished in areas where farmhands worked with both cows and horses. Direct transmission of cowpox from cow to cow had not been observed by Jenner; cowpox was the result of infection from a horse through human hands. The origin of cowpox was horsepox and in this sense they were varieties of the same disease.

Later in this same letter, Jenner discussed the link between cowpox and smallpox. The immediate context for his comments was the trials carried out by Woodville at the London Smallpox Hospital. Many patients who had been vaccinated by Woodville had generalized eruptions characteristic of smallpox. Jenner maintained that cowpox inoculation did not produce pustules all over the body, only at the site of vaccination, and he sought to explain at length the discrepancy between his and Woodville's experience:

> After reading my Publication and observing my assertion that the Cowpox does not produce Pustules, you may probably ere now have been much surpris'd at finding that they appear'd in considerable abundance among the Patients, inoculated with the virus taken from a Cow, at the Smallpox Hospital in London. However I presume this surprise will cease when you are inform'd that on the 5th day after the Cowpox virus had been inserted into one arm, the variolous virus was inserted into the other, in those whose eruptions resembled those of smallpox; & thus, in my opinion, the two diseases became blended. The Pustules, as the disease made its progress from one Patient to another soon began to decrease in number, and now they are become quite extinct, the matter producing appearances exactly similar to that newly taken from the Pock on the Nipple of the Cow. How extremely curious & singular is this Fact! Does it not almost tell us that

> the Cowpox is the original disease, the Smallpox a Variety & being the weaker is driven off by the stronger? Or is the latter assimilated by the former?[33]

As in the case of horsepox and cowpox, Jenner speculated that smallpox was the human variety of the same disease. By maintaining a common identity among horsepox, cowpox, and smallpox, Jenner forged a connection to earlier explanations for how inoculation worked.[34] If these diseases were merely varieties of the same species, then it was clear how cowpox would make a person exempt from a future attack of smallpox.

The other approach Jenner used to identify disease was to examine the origin and course of disease. In his pamphlet, Jenner raised the issue of what happens to a disease when it passes through different hosts: horses, cows, and humans. Some of Jenner's contemporaries were hesitant to accept his ideas. C.R. Aikin, a member of the Royal College of Surgeons in London, found Jenner's assertions about horsepox and cowpox 'the most dubious of all the facts that have been advanced on the subject'. Nonetheless, Aikin called for further studies to examine 'the particular modifications which a disease assumes, by passing through animals of different species', noting that these would contribute greatly to a better understanding of contagion.[35]

Pearson, whose ideas have been discussed earlier in this essay, also criticized Jenner for believing cowpox and smallpox to be varieties of the same disease. Pearson thought they were distinct species because they produced different symptoms. His approach was in line with Cullen's nosology and characteristic of one strand of eighteenth-century natural history. Pearson weighed in on the cases at the London Smallpox Hospital:

> Whether the vaccine poison, when it produces these cases resembling the small-pox, has really become, by composition or decomposition, variolous matter, is undetermined. If this should be found to be the case by future experiments, still we must consider the two poisons as of distinctly different species, on account of the different characters of the pustule in the small-pox and the cow-pox.[36]

Pearson provided a chemical analogy to drive home the point: magnesia and sulphate of magnesia are distinct species, even though magnesia can be turned into sulphate of magnesia through its union with sulphuric acid. Although Pearson rejected Jenner's theory that smallpox and cowpox were varieties of the same disease, he did not offer any explanation for how cowpox produced immunity to smallpox.[37]

Early attempts to make sense of vaccination addressed the relations between cowpox and smallpox. Jenner, the country doctor, used a broad, diachronic approach to explain the origin, course, and transformation of pox diseases. He was able to observe the appearance of and relations among horsepox, cowpox, and smallpox in his day-to-day practice in rural Gloucestershire. Pearson, by contrast, focused narrowly on symptomology and textbook nosology. His daily experience was with large numbers of hospital patients, not farm animals. Despite their disagreements about the nature of cowpox, for Jenner and his contemporaries, the key question regarding why vaccination worked belonged to natural history.

But more important than theory was the practical question: did it work? This question was addressed through patient trials, carried out in the countryside and the urban clinic. The trials were reported first as case histories and later as statistical accounts. These trials overwhelmingly demonstrated the safety and efficacy of vaccination and led to its

widespread adoption. The triumph of empiricism may not be surprising (especially to physicians), but its results in the case of vaccination were revolutionary.

Acknowledgements

I thank the participants of the conference and especially the editors of this volume for their perceptive and challenging questions. Finally, I am indebted to Paul Lucier.

Notes

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2 Francis M. Lobo, 'John Haygarth, Smallpox and Religious Dissent in Eighteenth-Century England', in Andrew Cunningham and Roger French (eds), *The Medical Enlightenment of the Eighteenth Century*, Cambridge; Cambridge University Press, 1990, pp. 217–53.

3 Genevieve Miller, *The Adoption of Inoculation for Smallpox in England and France,* Philadelphia, PA: University of Pennsylvania Press, 1957, pp. 80–91.

4 Andrea Rusnock, *Vital Accounts: Quantifying Health and Population in Eighteenth-Century England and France*, Cambridge: Cambridge University Press, 2002, pp. 49–70.

5 Edward Jenner, *An Inquiry into the Causes and Effects of the Variolae Vaccinae,* London: Sampson Low, 1798, p. 20.

6 George Pearson, *An Inquiry concerning the History of the Cow Pox; principally with a view to supersede and extinguish the Small Pox*, London: J. Johnson, 1798, p. 2.

7 Ibid., p. 5.

8 See, for example, Susan C. Lawrence, *Charitable Knowledge: Hospital Pupils and Practitioners in Eighteenth-Century London*, Cambridge: Cambridge University Press, 1996.

9 On hospital medicine see Erwin Ackerknecht, *Medicine at the Paris Hospital, 1794–1848,* Baltimore: Johns Hopkins Press, 1967; Michel Foucault, *The Birth of the Clinic*, trans. Alan Sheridan, New York: Vintage Books, 1975 [1963].

10 Othmar Keel, *L'Avènement de la Médecine Clinique Moderne en Europe 1750–1815, Politiques, institutions et savoirs*, Montréal: Presses de l'Université de Montréal, 2001, pp. 11–14. Also see Laurence Brockliss and Colin Jones, *The Medical World of Early Modern France*, Oxford: Clarendon Press, 1997, pp. 671–7.

11 Ulrich Tröhler, *"To Improve the Evidence of Medicine": The 18th Century British origins of a critical approach*, Edinburgh: Royal College of Physicians of Edinburgh, 2000, p. 3.

12 Andreas-Holger Maehle, *Drugs on Trial: Experimental Pharmacology and Therapeutic Innovation in the Eighteenth Century*, Amsterdam and Atlanta: Rodopi, 1999, p. 311. Maehle discusses the use of hospital trials to evaluate Peruvian bark on pp. 268–75.

13 William Woodville, *Reports of a Series of Inoculations for the Variolae Vaccinae, or Cow-pox; with Remarks and Observations on this Disease, Considered as a Substitute for the Small-pox,* London, 1799, reprinted in Edgar March Crookshank, *History and Pathology of Vaccination*, Philadelphia: P. Blackiston, Son, & Co., 1889, 2 vols., vol. 2.

14 Erna Lesky, *The Vienna Medical School of the 19th Century,* Baltimore and London: Johns Hopkins University Press, 1976, p. 14; H.J. Parish, *A History of Immunization,* Edinburgh and London: E. & S. Livingstone LTD, 1965, p. 27.

15 Boston Board of Health, *Announcement of Successful Experiment to prove the efficacy of Cow-pox*, 16 December 1802 [broadside]. See John B. Blake, *Public Health in the Town of Boston, 1630–1822*, Cambridge, MA: Harvard University Press, 1959, pp. 179–82.

16 *Rapport du Comité Central de Vaccine*, Paris: de l'Imprimerie de Gulleminet, AN XI (1803), pp. 12–18. See Robert G. Dunbar, 'The Introduction of the Practice of Vaccination into Napoleonic France', *Bulletin of the History of Medicine*, **10**, 1941, pp. 635–50; Elinor Maynell, 'French Reactions to Jenner's Discovery of Smallpox Vaccination: The Primary Sources', *Social History of Medicine*, **8**, 1995, pp. 285–303.

17 Tröhler, *"To Improve the Evidence of Medicine"* (n. 11), p. 13.

18 General Board of Health, *Papers Relating to the History and Practice of Vaccination*, presented to both Houses of Parliament by command of Her Majesty, London, 1857, cited in Hervé Bazin, *The Eradication of Smallpox: Edward Jenner and the First and Only Eradication of a Human Infectious Disease*, trans. Andrew and Glenise Morgan, San Diego, CA: Academic Press, 2000, p. 79.

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20 Anne Marie Moulin, 'La métaphore vaccine. De l'inoculation à la vaccinologie', *History and Philosophy of the Life Sciences*, **14**, 1992, pp. 271–97.

21 Arthur Silverstein, *A History of Immunology*, San Diego: Academic Press, 1989, p. 3.

22 Ibid., p. 1.

23 Thomas Nettleton, 'Part of a letter from Dr. Nettleton, Physician at Halifax, to Dr. Jurin, R.S. Secr concerning the Inoculation of the Small Pox, and the mortality of that Distemper in the natural Way', *Philosophical Transactions*, **32**, 1722, no. 374, p. 210. Emphasis in original.

24 Thomas Nettleton, 'A Letter from Dr. Nettleton, Physician at Halifax in Yorkshire, to Dr. Whitaker, concerning the Inoculation of the Small Pox', *Philosophical Transactions*, **32**, 1722, no. 370, p. 46.

25 [Cotton Mather], *An Account of the Method and the Success of Inoculating the Small-Pox, in Boston in New England,* London, 1722, pp. 7–8.

26 Silverstein, *A History of Immunology* (n. 21), pp. 11–14.

27 W.F. Bynum, 'Nosology', in W.F. Bynum and Roy Porter (eds), *Companion Encyclopedia of the History of Medicine*, 2 vols., London and New York: Routledge, 1993, vol. 1, pp. 335–56; Lester S. King, *Medical Thinking: A Historical Preface*, Princeton, NJ: Princeton University Press, 1982, pp. 105–27.

28 William Cullen, *Synopsis and Nosology, Being an Arrangement and Definition of Diseases*, second ed., trans. from Latin, Springfield, Conn: Edward Gray, 1793, pp. 17–18.

29 Other historians have discussed Jenner's emphasis on natural history. See, for example, Margaret Schibuk, 'The Search for Vaccinia', Ph.D. Thesis, Harvard University, 1986.

30 John Pickstone neatly summarizes the differences between these two approaches to natural history: '[N]atural history of particular places and times could sometimes be "in tension" with the kind of natural history which worked with "universal" taxonomies, e.g. of all flowering plants. The former study was central for country parsons and doctors who *lived* the natural history of their own localities, the latter for cosmopolitan travelers and curators who traveled to collect'. John V. Pickstone, *Ways of Knowing: A New History of Science, Technology and Medicine*, Chicago: University of Chicago Press, 2000, pp. 72–3. Emphasis in original.

31 Jenner, *An Inquiry* (n. 5), pp. 53–5; also see Derrick Baxby, *Jenner's Smallpox Vaccine: The Riddle of Vaccinia Virus and its Origin*, London: Heinemann Education Books, 1981, p. 68. In the third paragraph of Jenner's *Inquiry*, he asserted: 'The farriers call it the grease. It is an inflammation and swelling in the heel, from which issues matter possessing properties of a very peculiar kind, which seems capable of generating a disease in the human body (after it has undergone the modification which I shall presently speak of), which bears so strong a resemblance to the smallpox that I think it highly probable it may be the source of the disease'.

32 Edward Jenner to Jean de Carro, 27 November 1799; in Genevieve Miller (ed.), *Letters of Edward Jenner and Other Documents Concerning the Early History of Vaccination*, Baltimore: Johns Hopkins University Press, 1983, p. 10.

33 Ibid., pp. 10–11.

34 See Mirko D. Grmek, 'Les premières étapes de la vaccination: Mythe et histoire', in Anne Marie Moulin (ed.), *L'Aventure de la Vaccination*, Paris: Fayard, 1996, p. 51. This argument is also characteristic of the controversies that affected immunology in the late nineteenth and early twentieth centuries. See Pauline M.H. Mazumdar, *Species and Specificity: An Interpretation of the History of Immunology,* Cambridge: Cambridge University Press, 1995.

35 C.R. Aikin, *A Concise View of All the Most Important Facts which have hitherto appeared concerning the Cow-Pox*, second ed., corrected and enlarged, London: R. Phillips, 1801, p. 20.

36 George Pearson, 'A Communication from George Pearson, M.D. F.R.S. &c. Physician to St George's Hospital, &c. concerning the Eruptions resembling the Small-Pox, which sometimes appear in the Inoculated Vaccine Disease', *Philosophical Magazine*, **5**, January 1800, pp. 316-17.

37 Two years later, after many more clinical trials, Pearson was confident in his belief that the two diseases were distinct species. George Pearson, *An Examination of the Report of the Committee of the House of Commons on the Claims of Remuneration for the Vaccine Inoculation; containing a Statement of The Principal Historical Facts of the Vaccina*, London: J. Johnson, 1802, p. 119. The controversy over what occurred at the London Smallpox Hospital has continued into the twentieth century, discussed most recently by Baxby, *Jenner's Smallpox Vaccine* (n. 31); Peter Razzell, *Edward Jenner's Cowpox Vaccine: The History of a Medical Myth*, Firle, England: Caliban Books, 1977; and Schibuk, 'The Search for Vaccinia' (n. 29).

CHAPTER THREE

Risk, Efficacy and Viral Attenuation in Debates over Smallpox Vaccination in Montreal, 1870–1877

Jennifer Keelan

Historians, such as Anne Marie Moulin, have drawn rather sharp distinctions between immunology and vaccinology, separating the theoretical exploration of cellular and serological immunity from the practical manipulations of vaccine material for disease prevention. Yet, until the last decade of the nineteenth century, concepts of immunity and nascent immunology were shaped primarily by the vaccinator's lancet.[1] Warwick Anderson, Myles Jackson and Barbara Guttman Rosenkrantz, in their article 'Toward an Unnatural History of Immunology', call for more research outside the entrenched genealogy of ideas that has come to define the history of immunology.[2] This paper follows their lead in focusing on the inter-connected history of the developments in theoretical concepts of immunity and the methods for measuring and controlling vaccine quality achieved through the nineteenth century practice of smallpox vaccination.

The first theoretical explanation of how vaccination worked was advanced by Edward Jenner himself in his 1798 treatise on vaccination.[3] He argued that vaccination was a human infection with a modified form of smallpox found in cows which he called *variola vaccinae* (literally smallpox of the cow). He observed that vaccination provided as much protection as an infection with human smallpox but invariably produced a mild infection that was not contagious. His empirical observations were bolstered by large-scale clinical trials of vaccination in smallpox hospitals (see Rusnock this volume). Data collected in smallpox hospital trials, in the early years following the introduction of vaccination, generally confirmed Jenner's claims that vaccinated patients showed the same peculiar immunity to smallpox as those who had naturally caught the disease, or those who had been artificially inoculated with smallpox, but without the associated risks of death or disfigurement. Jenner's emphasis on the aetiology of *variola vaccinae* as an attenuated form of human smallpox was initially overshadowed by the clear and convincing body of empirical evidence supporting the practice.

However, by the 1830s, difficulties in procuring and propagating effective vaccine and reports of smallpox in patients who had been successfully vaccinated complicated the clinical picture of vaccination and its effect on smallpox. Heterogeneity in vaccination practices both locally and internationally further fuelled a debate over which vaccines and what techniques worked best, and some physicians began to question whether vaccination really worked at all. The attempts to sort out the technical problems took on a particularly public dimension in regions where vaccination was already actively

resisted by the public. The increasingly diverse experiences with vaccination and popular resistance to the technology led to intense public scrutiny of the practice and forced physicians to re-examine the theoretical nature of vaccine-induced immunity.

The socio-political context of debates over vaccination has been explored by Sanjoy Bhattacharya, in his work on vaccination in colonial India, and by Nadja Durbach, in her examination of the class dimensions that shaped debates over compulsory vaccination laws in England.[4] The combination of socio-political and medico-technical problems confronting advocates of universal vaccination was also strikingly evident in cities like Montreal where political tensions between French Catholics and English Protestants made compulsory smallpox vaccination a wedge issue in local politics. This tension came to a head in the early 1870s when municipal public vaccinators, lamenting the high infant mortality rate and poor uptake of vaccination among the French Canadians, focused their attention on the working-class French Canadian districts of Montreal and attempted to enforce compulsory infant vaccination. Discord between French Catholics and English Protestants was so high that it was reported in the *New York Times* that at the height of the smallpox epidemic, when the dog guarding the Catholic cemetery died, the French populace refused to allow a dog from the Protestant cemetery to stand guard over their dead.[5] At the same time there was a crisis in confidence in the technology itself. Physicians complained of a high rate of failure for public and private smallpox vaccinations and there was widespread distrust of public vaccinators and their vaccine supply.[6] The myriad problems with procuring safe and effective vaccine were highlighted during the smallpox pandemic of 1870–2 and remained critical issues throughout the 1870s. Annual epidemics of smallpox consistently inflated Montreal's infant and total mortality above other cities like London and Paris.[7] The ensuing debate over the usefulness of vaccination quickly polarized Montreal physicians into camps of pro- and anti-vaccinationists.[8]

The study of both the content and the context of this debate can serve to frame – or perhaps problematize – Moulin's description of the paradox of 'immunization without immunology'.[9] Historians Michael Farley, Peter Keating and Othmar Keel have sketched out the technical, political and cultural difficulties faced by those implementing municipal vaccine campaigns in Montreal and, in the process, have highlighted the fact that physicians were concerned about the type and quality of the vaccine used. But they did not explicitly relate the theoretical commitment to viral attenuation with vaccination practice nor did they examine its impact on how the empirical data was constructed and interpreted.[10] Though it was not a predecessor of any significant breakthrough in twentieth-century immunology, the theory of viral attenuation (the idea that the virulence of infectious contagions could be weakened if specially cultivated) encapsulated nineteenth-century concepts of immunity. Attenuation theory was more than an amorphous metaphor.[11] It was the working language that framed vaccination for both supporters and detractors. Problems with the technology in the field both framed and were framed by the theoretical understanding of vaccine-induced immunity and its attendant risks. Just as Olga Amsterdamska has argued that the way in which socially relevant problems are selected and formulated as research questions are constrained by contemporary theoretical conceptions, I argue that there was a complex and recursive relationship between the practical problems vaccinators faced in assessing and implementing safe and effective vaccination and theories of viral attenuation.[12]

Interestingly enough, both supporters and critics of vaccination used concepts of viral attenuation to describe the varied clinical presentations of smallpox and to account for the inconsistent success of vaccination. Pro-vaccinationists tended to argue that what appeared to be the large scale failure of vaccination was a result of variable attenuation of the vaccine which altered its potency or virulence, but they increasingly conceived of wild smallpox as a relatively fixed species. By 'fixing the contagion', the effectiveness of the vaccine during a particular epidemic could be measured through standard hospital data, and the technique of vaccination could be improved accordingly. Anti-vaccinationists maintained that wild smallpox was variously attenuated as it spread through human and animal populations and further that there was a range in human susceptibility to the disease. The protective effects ascribed to vaccination were simply a manifestation of natural changes in one or the other.[13] Anti-vaccinationists were particularly successful in using concepts of attenuation to provide an alternative interpretation of data used to support vaccine's efficacy. Theoretical arguments about how vaccination worked underpinned the fundamental belief or disbelief in vaccination which in turn shaped the reading of nineteenth-century data and profoundly shaped the assessment of both risk from the vaccine and its ability to protect the individual against smallpox.

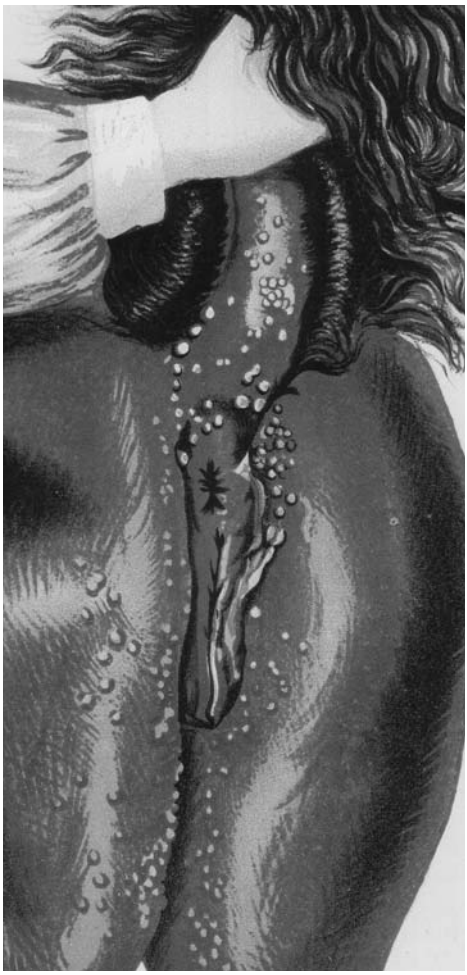
Nineteenth-century Attenuation Theory

Jenner did not invent the concept of viral attenuation. Descriptions of attenuation can be found in many eighteenth-century treatises on inoculation including the following passage written by the Tuscan inoculator Angelo Gatti:

> I think that a variolous matter which has passed through several bodies … becomes weaker than wild smallpox and in passing through different chosen bodies, could insensibly acquire a better nature, could come to terms, so to say, with the human body, be weakened and insensibly altered by these successive transplantations, and finally to cease playing such a considerable role among contagious poisons.[14]

Jenner believed that cowpox outbreaks were the result of a spontaneous chain of infections that originated in cases of human smallpox, spread through direct contact to horses, then to cows and transmitted back to humans. It was not the symptoms of the diseases cowpox, horsepox, and smallpox that led Jenner to embrace this theory, although all produced fluid filled pustules (see Figure 3.1), but rather his careful tracing of the natural history of several cowpox outbreaks. The rarity of cowpox outbreaks and the unusual chain of transmission from horses to cows to dairymaids, noted in his case studies, convinced Jenner that a complex chain of events was required to produce the benign human cowpox infection that folklore credited as a natural and sure protection against smallpox.

Implicit in Jenner's theory was a process of attenuation whereby a single smallpox contagion could, through a natural process of inter-species infection, be permanently transformed. Once this process of transformation occurred, the contagion would remain essentially stable if propagated solely from human to human. Attenuation theory also implied that each species of contagion was associated with a 'target host', in which the contagion could grow and express its fullest potential or virulence. Jenner's ideas about



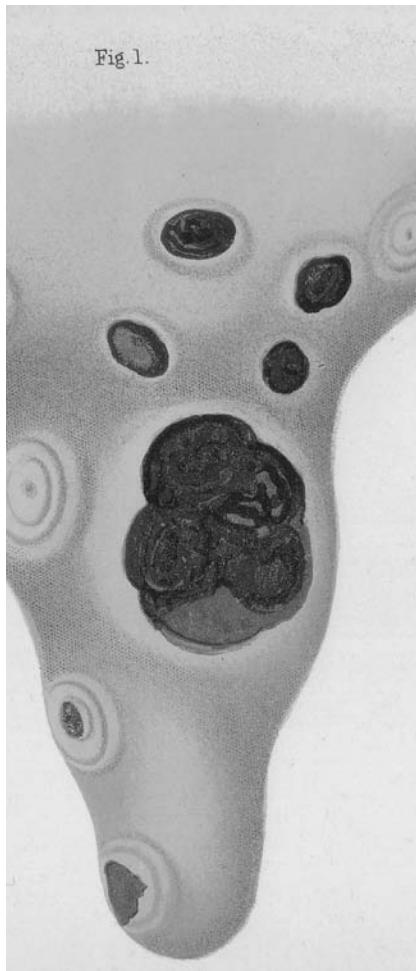


Figure 3.1 a,b Spontaneous horsepox (above, left [3.1a]), and spontaneous cowpox (above, right [3.1b]. Source: Edgar March Crookshank, *History and Pathology of Vaccination* (1889), Plates 2 and 19.

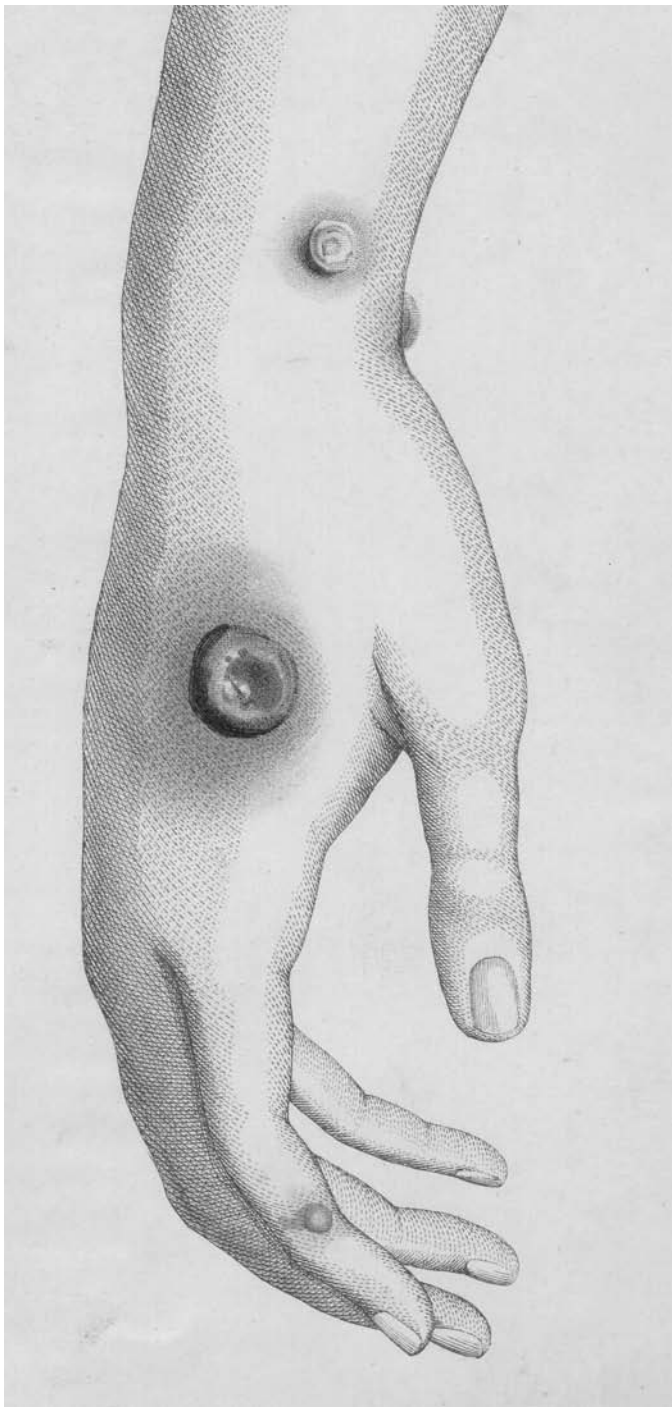


Figure 3.1c A spontaneous human infection. Source: Edgar March Crookshank, *History and Pathology of Vaccination*, (1889), Plate 23.

attenuation were taken up by leading vaccinators in Canada, as illustrated by this quote from a treatise on vaccination written by Montreal physician and public vaccinator William E. Bessey:

> [Jenner's observations] led him to perceive in cow-pox, small-pox in its mildest possible form, or in other words that pox was pox, one and the same, no matter upon what animal it might make its appearance and, only modified in character and severity by the animal through which it happened to be transmitted … [cowpox] is identical with and only a modified form of smallpox.[15]

It was imagined that the growth and propagation of the contagion depended on the presence of a vital nutrient that was exhausted during the course of the infection, hence rendering the person immune to re-infection. This theory of exhaustion was the most common explanation for how vaccination actually produced immunity in the individual:

> *Vaccinia* is but one member of a group of exanthemas among which non-reoccurrence is the rule, and a second attack in the life-time the exception; and another is small-pox; with which vaccinia, as one of the varioloid maladies, has the very closest relationship; so close, that the vaccine disease, when undergone, destroys that in the human system which imparts to it the capability of developing vaccinia.[16]

By the 1830s, over a thousand generations, taken from the various *variola vaccinae* (cowpox) stocks, had been produced by serially propagating cowpox solely in humans (each generation required about a week to mature). Preserving this humanized vaccine on threads, glass or on ivory points was fraught with difficulties and more often these techniques failed to produce or maintain a good vaccine supply. The nineteenth-century trade in vaccine lymph highlights the technical problems vaccinators faced when distributing vaccine to India, China, Japan, North America and elsewhere. Margaret Schibuk has described the problem that vaccinators faced trying to maintain the original stock vaccines distributed by Jenner or other strains certified as authentic cowpox by his followers.[17] Some physicians believed that the serial propagation of vaccine in humans over time led to a gradual 'humanizing' or weakening of the strain, in a process similar to the original inter-species attenuation. This meant that the vaccine strain would ultimately fail to produce a protective infection after an unknown number of generations. Certainly potent vaccine strains were difficult to maintain. Physicians required a steady stream of susceptible children to grow their vaccine, in a process called arm-to-arm or 'Jennerian' vaccination, and after hundreds of generations, some vaccinators found that their harvested vaccine material diminished in power.

Technical problems with maintaining vaccine stocks first drove physicians to seek out new sources of spontaneous cowpox, but in the absence of natural sources of vaccine lymph, vaccine manufacturers began to experiment with artificial attenuation. They attempted to either re-invigorate the humanized vaccine supply by growing it in the cow, or they tried to produce an entirely new source of *variola vaccinae* (cowpox) by artificially replicating the inter-species cycle of infection that Jenner described.[18]

Empirical research into vaccine potency and the experiments with the artificial production of stock vaccine via the retro-vaccination of wild smallpox were clearly

driven by the theory of viral attenuation. During the 1830s and 1840s, for example, the English vaccine farmer Robert Ceely and the chemist John Badcock performed a variety of experiments to refresh the source lymph and to increase its virulence to a level where it would provide better protection.[19] Human or wild smallpox was far more common than cowpox, and if wild smallpox could be used to create stock lymph, the pressure to find natural cowpox stocks would be eased. Reports that *variola vaccinae* could be created by inoculating cows with wild smallpox were widespread and reported in the Montreal literature. The principle of attenuation was generally, though not universally, accepted in Montreal, as in Britain and the German-speaking territories, until well into the twentieth century.[20] For example, in *The Principles and Practice of Medicine,* William Osler stated that, 'The weight of evidence favours the view that cow-pox and horse-pox are variola modified by transmission'.[21] While admittedly a more difficult technique that achieved less success than the use of 'true cowpox', manufacturers claimed that they had successfully changed smallpox into cowpox to produce many lots of vaccine lymph.[22]

If cowpox was simply smallpox attenuated by growth in cows, then the exhaustion theory provided a coherent explanation for vaccine-induced immunity. This physical law of immunity, which dictated that individuals were protected against repeated infection with the same contagion, neatly tied together the taxonomy of the pox viruses with a physical mechanism of immunity, but only if vaccine and smallpox were basically the same contagion altered by the process of attenuation.

The Principles of Vaccination and the Assessment of Vaccine's Efficacy

While the theory of viral attenuation supported a natural law for immunity 'once infected forever protected', the arguments used to support intrusive government policies like compulsory infant vaccination relied instead on the empirical and statistical support for the practice. As was mentioned earlier, the simplistic assertion that vaccination provided lifelong immunity against smallpox was challenged by contrary evidence that accumulated during the nineteenth century. Patients with a confirmed case of spontaneous cowpox infection reportedly caught smallpox, and the reverse scenario was also observed. Cases were also reported where individuals whose vaccination was confirmed with smallpox inoculation (an inoculation challenge) still caught a serious form of smallpox. There even seemed to be people naturally immune to both smallpox and cowpox – even with the best lymph and the most renowned vaccinator, the vaccine would reportedly not 'take' among some children who had never had either smallpox or cowpox. In Canada, for example, there were numerous reports of medical staff working in smallpox wards, such as the Montreal physician Dr P.E. Plante, who refused vaccination and apparently never caught the disease.[23] Vaccination seemed to *sometimes* provide *specific* protection against smallpox, but not in all people, and some people seemed naturally immune. Beyond the technical difficulties of achieving a proper vaccination, it became clear to critics that vaccination often failed to protect people against smallpox. Still, Dr William Hales Hingston, a staunch advocate of vaccination, and Mayor of Montreal from 1875 to 1877, argued rather unrealistically that proper vaccination gave as much protection to the individual as a primary attack of smallpox, and further that vaccination was even more effective in mitigating the disease than a primary infection.[24]

But how was a 'proper' vaccination defined? Smallpox itself was mutable through the natural processes of attenuation and this might account for a variation in its virulence or infectivity, independent of any effect produced by vaccination. Attenuation was extremely useful in explaining specific immunity, but by introducing the idea of a mutable contagion, it undermined how clinical categories were constructed and how the assessment of vaccine's efficacy could be read from empirical data. More puzzling, an unvaccinated person infected with one form of smallpox, such as a mild but distinct smallpox case, could be shown to infect another unvaccinated person with a more serious form of smallpox, thus raising the question of how Hingston could use clinical data to judge vaccine's ability to mitigate the disease.

As Andrea Rusnock has shown, the basic mode of statistic analysis used to study inoculation and vaccination remained unchanged throughout the nineteenth century. It depended on the mathematical techniques developed for life insurance rates or 'merchants' logic'.[25] The kinds of analysis used to determine whether or not inoculation should be used relied on key assumptions concerning the perceived risk of catching smallpox, the risk of dying from smallpox, and finally the risk of catching smallpox from inoculation or vaccination. These categories tended to be binary: subjects were classified as either 'protected', or 'unprotected', and either 'died of smallpox', or 'survived smallpox'. These categories, designed for life tables, were often inappropriately simplistic for assessing smallpox and vaccination. The raw data were ambiguous. Data that seemed to correlate a decline in smallpox with the introduction of vaccination were problematic, as smallpox appeared to have a complex natural pattern where it periodically waxed and waned. The character of its virulence seemed to oscillate as well. If the statistical determination of the effects of vaccination in mitigating smallpox depended on identifying good from bad vaccinations, and good and bad vaccinations were determined by the presumed mitigation of the severity of the resultant disease, the result was an intractable tautology.

An example of how this tautology shaped the reading of epidemiological data is demonstrated in this excerpt from the *Canadian Journal of Medical Sciences* of 1876:

> We have recently passed through a pretty severe epidemic, in which a large number have been attacked; and we think that two things have been amply demonstrated. First, the great majority of those who have passed through critical attacks have been *unvaccinated, indifferently vaccinated or not successfully vaccinated, for many years previously* [emphasis added]. Secondly, it has been clearly shown that where persons recently vaccinated successfully have been attacked, they have passed through a *modified form of the disease* [emphasis added]. It has been further shown pretty conclusively that most persons exposed, but recently protected, have escaped altogether.[26]

At first glance, this seems perfectly supported and reasonable. The critical elements, however, relate to the tricky concepts of what defined *successful* and *unsuccessful* vaccination. Physicians had yet to develop a system for predicting whether a vaccination was real or spurious.[27]

Though it was often argued that a good vaccination was defined by its ability to perfectly protect a person from catching smallpox, or it at least protected as much as a primary infection, data taken from smallpox hospitals did not support these assertions. Merely having been vaccinated did not necessarily prevent an individual from catching

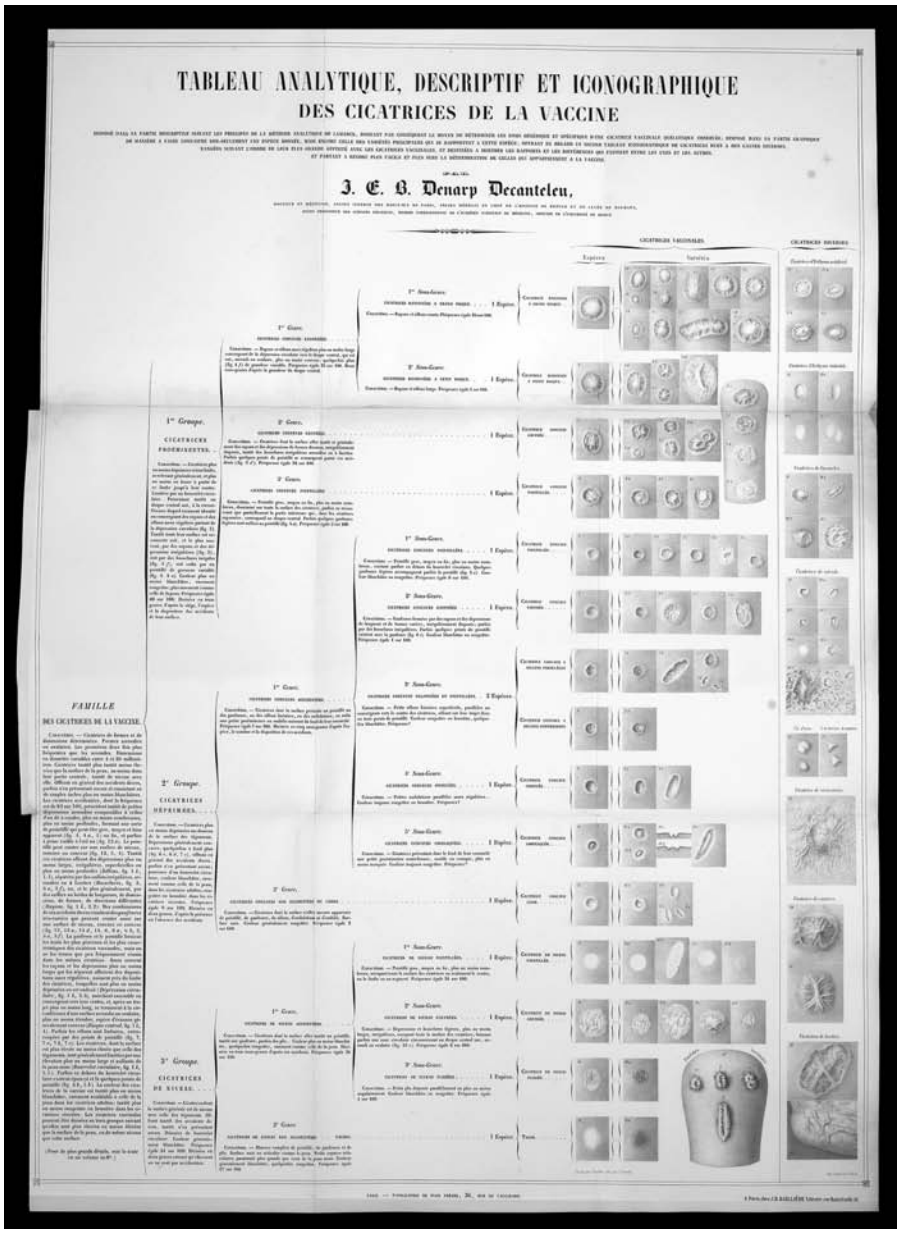


Figure 3.2 Lithograph of J.E.B. Denarp-Decanteleu's 'Analytic, Descriptive, and Iconographic Table of Vaccine Scars'. Source: reproduced in Martin, *On Animal Vaccination*, Boston, 1878, n. 29.

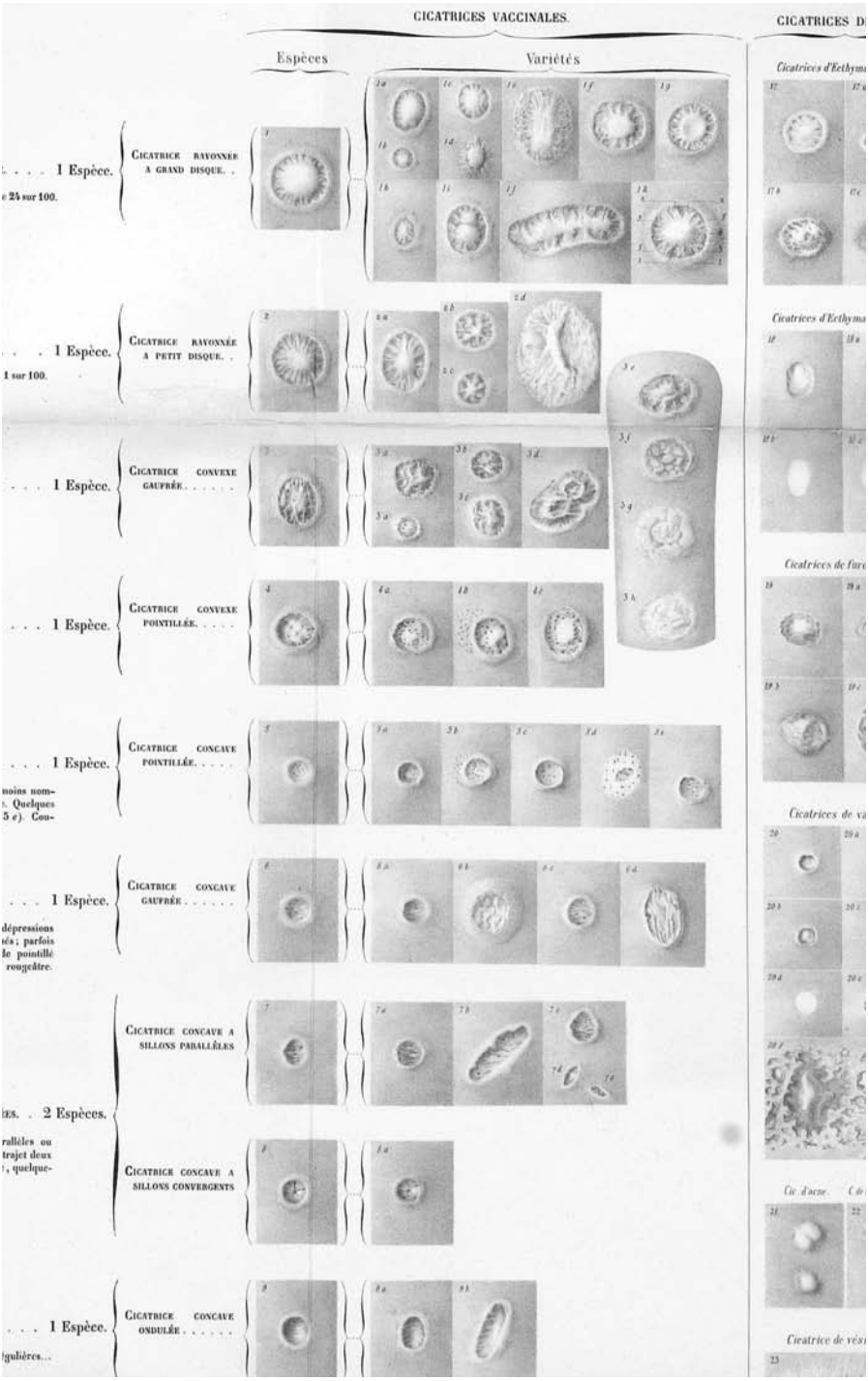


Figure 3.2 Detail.

the disease or even dying from it. Admission data from British smallpox hospitals, and local data from Montreal, frequently reported that only 50 per cent of their patients were not vaccinated, and in the same time period, the number of unvaccinated infants in Montreal was generally estimated to be higher than 50 per cent.[28] Even the data of esteemed pro-vaccinationists did not always support vaccine's efficacy without a number of imposed qualifiers.

If you were vaccinated in the late nineteenth century, how would you or your physician be able to predict whether or not you would likely contract smallpox or die from the disease? By the 1870s, the number and character of vaccine scars or 'cicatrices' were seen as critical markers for vaccine's efficacy. A taxonomy of smallpox scars was developed by the French vaccinator J.E.B. Denarp-Decanteleu and popularized by the American vaccine manufacturer Henry Austin Martin.[29] Martin had Denarp-Decanteleu's scar taxonomy re-published and distributed across North America in an attempt to show how different circulating vaccines caused distinctly different vaccine scars. He particularly wanted to show the superiority of vaccine propagated solely in cows (animal vaccine) over more traditional Jennerian vaccination, propagated arm-to-arm. The folio also instructed the average physician how to distinguish the marks of a true vaccine scar from other scars caused by other infections or injuries, such as skin burns. The large table-sized lithograph illustrated over one hundred different types of vaccine scars divided into families, subfamilies, groups, and types based on their physical characteristics (See Figure 3.2). Martin argued that the scar types could be used to distinguish between different types of vaccines and this could be correlated with the degree of attenuation of the vaccine and ultimately its potency and effectiveness (the more attenuated, the weaker the vaccine). However, to use Denarp-Decanteleu's taxonomy to assess the quality of vaccine would require that fine visual distinctions be made between scars, skills few physicians likely possessed.[30]

The number of scars was far easier to tabulate. It corresponded with the number of discrete colonies raised during a primary vaccination. The recorded number of vaccine scars could but did not usually indicate a second or third vaccination, since re-vaccinations rarely raised good vaccine scars. Thus, four pronounced smallpox scars likely resulted from four distinct colonies raised during a single vaccination procedure as seen at right (Figure 3.3).

Figure 3.3 This photo shows a 'typical' good vaccination of the late 1880s. Notice the five colonies raised on this primary vaccination. These would each form a separate vaccine scar. Source: S.M. Copeman, *Vaccination; its Natural History and Pathology*, London: MacMillan, 1889, Plate 10.

How vaccine scars were counted is important contextual information when trying to decipher nineteenth-century smallpox hospital records. Hospital data showed that there was a marked difference in the sign of protection against smallpox given respectively by four, three, two, and one scar. The incidence of patients admitted with four scars differed from those with only one scar by a factor of fourteen, and the incidence of those admitted who had been vaccinated but did not have a clear scar was forty-two times larger than the population admitted with four clear vaccine scars.[31]

The London vaccinator J.F. Marson was one of the earliest respected vaccinators to advocate multiple cicatrices (scars). Using data from the London Smallpox Hospital, he correlated the number of prominent cicatrices with a decreased mortality rate from smallpox and a decrease in the severity of the disease. However, while vaccinated patients were more likely to suffer from the mildest form of smallpox (varioloid) and these cases became synonymous with the category 'vaccine-modified smallpox', he claimed that vaccination did not invariably prevent any of the more life-threatening forms of smallpox, though it did decrease the likelihood of dying from confluent or fatal smallpox:

> When one or two cicatrices can but just be seen, or doubtfully seen, the case may be as severe as if there had been no vaccination at all, the eruption pass through its several stages quite unmodified and the disease proceed, terminate, uninfluenced, in any way by previous vaccination. [32]

Marson stated that an acceptable failure rate for vaccination was, given his experience, about 1 in 50. However, he lamented that with current practices (untrained physicians using poor technique and weak lymph) the real failure rate for vaccination was closer to 1 in 15. 'Operations for hernia and for stone, for instance, if roughly, carelessly, and badly done, end badly; so it is with vaccination: and so far as the public is concerned, it is quite as objectionable to them, no doubt, to die of Small-pox because they have been badly and carelessly vaccinated'.[33]

1	Unvaccinated		35
2	Stated to have been vaccinated, but having no cicatrix		23.57
3	Vaccinated		
	a	Having one vaccine cicatrix	7.73
	b	Having two vaccine cicatrices	4.70
	c	Having three vaccine cicatrices	1.95
	d	Having four or more vaccine cicatrices	0.55
	α	Having well-marked cicatrices	2.52
	β	Having badly-marked cicatrices	8.82
4	Having previously had Small-pox		19

Figure 3.4 Marson's data from the London Smallpox Hospital, giving percentages of all admissions vaccinated vs unvaccinated 1836–55. Note that the 35% unvaccinated patients is compared to the 23.57% categorized as unvaccinated because they had no scar and to the remainder categorized as having clinically verified vaccinations (one or more clear scars). Approximately 15% of those vaccinated had scars, but only 3% had what Marson considered a true sign of protection. From Marson, 'Smallpox', in Reynolds (ed.), *System of Medicine,* Vol. 1. London: Macmillan, 1876. p. 264.

Marson emphasized that as long as the source of the variability of clinical presentations could be attributed to spurious vaccinations (the 23.57 % in this data set), it would be impossible to objectively quantify the effect of vaccination (see Figure 3.4). Categorizing vaccinations as 'true' or 'false' helped stabilize the definition of clinical syndromes of smallpox, which, in turn, became an index of the vaccine's efficacy.

There were critical problems with this kind of analysis. Anti-vaccinationists were quick to point out that the number of people in the population with four good scars was a very small fraction of the overall number vaccinated during this period. They credibly argued that because of different styles of vaccinating, only a minority of vaccinators raised four vaccine colonies in a single vaccination, so the one, two, and three scar theory simply reflected the proportions of these results (raising one, two or more marks), and had nothing to do with the relative protection offered by the vaccine. They also used similar arguments to dismiss the statistical data showing that the lowest incidence of mortality was among those with four clear vaccination marks.

The Montreal Debate: Risk, Efficacy, and Attenuation

Between 1870 and 1872, a severe smallpox epidemic ripped through Europe and the United Kingdom, where vaccination programs were far more advanced. In 1872, the epidemic hit Montreal, a city of 120,000, killing 897 people. Two years before the European pandemic, a prominent Montreal surgeon, Dr Joseph Emery Coderre, gave a talk to the *Institut Médicale* on the ill effects of vaccination. Of his eleven children, two died shortly after being vaccinated.[34] Having renounced vaccination forever, he now appeared before an audience of physicians to persuade them that the dangers of vaccination had been grossly underestimated.

Coderre would become the voice of French Canadian anti-vaccinationism until his death in 1888. Sometime in 1872, he and a group of Montreal physicians formed the first Canadian Anti-vaccination League. He promulgated his anti-vaccination views as a co-founder of the Montreal Medical Society, and used his position, and the journal, *L'Union médicale du Canada*, to disseminate anti-vaccination ideas to the profession. Coderre's reputation as a physician, skilled surgeon, and teacher does not appear to have been sullied by his staunch anti-vaccinationism. For 43 years he was a fixture at the Hôtel Dieu, and by all accounts had an extremely lucrative surgical practice.[35]

The debate intensified on 20 December 1871, when many physicians present at a meeting of the Montreal Medical Society expressed concerns over the quality and nature of the vaccine. Dr A.T. Brosseau presented six cases of smallpox among the vaccinated, of which two were severe and one ended in death. He also noted that an unvaccinated child in his practice escaped the disease altogether.[36] Despite his experience, he was not willing to pronounce vaccination useless, but rather argued that the vaccine in use in Montreal was of an inferior nature.[37] Dr L.A.E. Desjardins agreed that it was not the underlying principle of vaccination that was in question, only its implementation. With the present technology, however, vaccination was neither preventative nor preservative. Cases of smallpox among the vaccinated did not appear to be less severe than among the unvaccinated:

> I am for vaccination in principle, but I have doubts about the effectiveness of the vaccine as it has been used here. Most of the smallpox cases under my care had been vaccinated and I did not notice that [cases of] discrete smallpox or confluent smallpox were influenced by this method.[38]

Dr G. Grenier added that the protective quality of vaccine stock must somehow fade or become attenuated after an unspecified number of life cycles through individuals and animals, causing the virus to lose all protective potency and leaving the vaccinated person as unprotected as the unvaccinated.[39] In the same discussion, Dr P.E. Plante commented that the current vaccine stock in use appeared to actually be dangerous. He had vaccinated fifty cases in his first year of practice, of which four had reacted severely to the operation – and two cases resulted in gangrene, for which the normal treatment would have been amputation of the arm.[40] He, like Brosseau, would not continue to vaccinate under these conditions: 'I believe in the transmission of syphilis through vaccination and have ceased, for the time being, to vaccinate'.[41] He also argued against suggestions that that the current lymph could somehow be restored by passing it back through the cow to regain its virulence through a process of reverse attenuation.[42]

In this discussion, the source and strength of the vaccine stock lymph was seen as a critical variable. While all agreed that there was a problem procuring 'good' vaccine, they could not agree which stock vaccine produced the most reliable results. For some, the idiosyncratic results were caused by the use of humanized vaccine that had become heavily attenuated by serial passage through humans (a process Jenner disputed could occur), and for others, vaccine taken directly from the cow (animal vaccine), was not attenuated enough to be used safely. While pure animal vaccine was preferred by some leading vaccine manufacturers like Bessey and Martin, many physicians reported that it caused extreme reactions and constitutional symptoms such as fever and excessive swellings under the arm.[43] Despite the fact that many physicians testified that they had not had much personal success with vaccination, they still maintained that vaccination-induced immunity was a robust phenomenon. Explaining the failures in their own practices meant re-examining the technology and seeking out a vaccine that worked in the field. Their understanding of why some vaccines were superior to others remained bound to the concept of attenuation.

In a series of lectures given before the Montreal Medical Society in January and February of 1872, Coderre outlined the problems with trying to assess the efficacy of vaccination without taking into consideration the full implications of attenuation theory, with incomplete statistics, and far too much implicit faith in the procedure.[44] In an exploration of how belief in vaccination influenced the reading of the data, Coderre began a systematic re-analysis of typical pro-vaccinationist data. In a report taken from the *Paris Hospital Gazette*, smallpox data on French soldiers admitted during the siege of Paris was recapitulated. Of 504 cases of smallpox tabulated in the report, nine-tenths had been vaccinated, one-sixth re-vaccinated, five-eighths caught mild smallpox (*variole légère*), and there were few deaths among the vaccinated. The article's original author had interpreted this as proof of vaccine's efficacy, but Coderre came to a completely different conclusion. He took it as self-evident that vaccination did not prevent the vaccinated from catching smallpox, as nine-tenths of those admitted had been vaccinated. He further argued that this data could not be used to prove the *mitigation* of the disease either.

The argument that vaccination caused milder cases of smallpox among the vaccinated made no sense if there was no difference in the attack rate between the two groups. How could vaccination mitigate the disease without preventing it in greater proportions among the vaccinated compared to those who were unvaccinated? It is important to note that while annual admissions to Montreal smallpox hospitals frequently reported that unvaccinated patients outnumbered the vaccinated by a ratio of 2:1, without an accurate estimate of how many people in Montreal were actually vaccinated, this ratio could arguably represent the poor uptake of vaccination rather than the decreased susceptibility to smallpox among the vaccinated, that is, there may be twice as many unvaccinated as vaccinated in the general population. Also, hospital data from Montreal was rarely complete enough to allow for a direct comparison between vaccinated and unvaccinated groups since vaccination data were routinely missing for nearly a third of smallpox patients and 'doubtful cases' were combined with cases where the vaccination status was unknown.

What pro-vaccinationists like to call vaccine-modified smallpox, argued Coderre, was a manifestation of the complex and poorly understood interaction between a changeable contagion and the particular constitution of the host, a phenomenon well documented in the natural state of the disease, as well as among the unvaccinated.[45] Smallpox was a disease that did discriminate against the poor, malnourished, and ill-kempt of society. The severity of smallpox among the poor living in crowded tenement housing blocks was undoubtedly exacerbated by the social conditions of the victims and their poor and vulnerable constitutions.

The second part of Coderre's argument drew explicitly on writings of the French vaccinator and theorist J. DePaul.[46] DePaul, like Jenner, believed that pox viruses formed a continuous species that were communicable among a wide range of host populations. DePaul argued that cows, horses, ewes, and many other domestic animals could catch smallpox from humans, and communicate it among their herds. Departing from Jenner, DePaul, and most provaccinationists, Coderre argued that vaccine was clearly communicable, and recently vaccinated people could spread the infection to other parts of their bodies and to other people and animals.[47] He cited a case reported by Ceely in which a woman infected with smallpox appeared to have transmitted classic cowpox to her five cows. Smallpox epidemics appeared and disappeared in human populations, but Coderre did not believe that they occurred spontaneously. He argued instead that smallpox circulated in different forms among many animals, and that it was transmitted in epidemic situations via animals associated with humans. By its growth in different animals, the virus could undergo changes and become more or less virulent to humans, depending both on the host and the conditions under which it grew. Coderre believed that the process of viral attenuation was reversible. Cowpox was not merely smallpox of the cow, it could revert to its more lethal wild type.[48] The attenuation of the virus as it passed from animal to human was unpredictable and unstable.[49]

Coderre felt that vaccination not only could revert to a wild type and spread smallpox, but it could spread any other contagious disease present along with it.[50] Most vaccination was performed arm-to-arm in Canada until the mid-1880s, hence contagious diseases were thought to be spread if the vaccinator chose to propagate the virus in an unhealthy child. Coderre related a particular set of complications from his own vaccination days when he was vaccinating with a rather antique lymph. Five infants

from four separate families suffered similar and severe reactions from his vaccine. Large pustules developed on the vaccinated arm accompanied by smaller pustules on the arm and face. Four of the five children died before reaching the age of two and one half years. Coderre also felt that the rise in cases of pulmonary tuberculosis in infants, and of cases of scrofula, was linked to infant vaccination.[51] He argued that the difference in deaths among the vaccinated and unvaccinated was too small to put infants at risk of complications from a vaccine that could revert back into a serious disease, or expose the child to other serious contagious diseases.

To summarize Coderre's understanding of the comparative risks of vaccination versus that of contracting smallpox (which was hardly ubiquitous in Montreal), he argued that the known risk of vaccination was far greater than the possibility that a child would contract smallpox and be harmed by it:

> Is the disease inevitable? Is the cure certain? In the first case, one can say that the large number of people never catch smallpox; and in the second, on the contrary, the great number who catch smallpox has been vaccinated.[52]

Coderre's series of lectures in 1868 and 1872 won him a number of allies in his anti-vaccination work. Tensions between the pro- and anti-vaccinationists mounted when new measures to record vital statistics were proposed based on the recommendations of the newly-appointed Public Health Officer, Dr A.B. LaRocque. It was also proposed that the list of births be given to the public vaccinators such that vaccination could be performed before the child was four months old. Up to this point, any discussion about compulsory vaccination was truly academic – the decision was up to the discretion of the individual and their physician, as there were no existing municipal records that consolidated lists of children and verified their vaccination status. The spectre of compulsory vaccination intensified the debate over the relationship between smallpox and vaccine.

In 1875, the staunch pro-vaccinationist Hingston was elected Mayor of Montreal. Smallpox sharpened Hingston's interest in the lamentable state of public health in Montreal and made him a passionate advocate for reform. He was an energetic leader who was convinced that smallpox could be eradicated if only the municipal government followed England's lead and authorized public vaccinators and sanitary police to enforce compulsory vaccination. He regularized the health committee of the city by appointing LaRocque as the Medical Health Officer of Montreal, formalizing his position with a proper salary.[53] He countered Coderre's series of frightful broadsheets depicting vaccine-injured children, which were prominently displayed in public places in French wards (in shop windows), and the vitriolic anti-vaccinationists' speeches, with his own campaign supporting vaccination.[54] In 1876, Hingston was featured on the front page of the *Canada Illustrated News*. The cartoon depicted Hingston as St George, slaying the dragon smallpox (see Figure 3.5).

Both LaRocque and Hingston waged a public war against Coderre over the issue of vaccine safety and compulsory vaccination. Given that compulsory vaccination was a matter of public policy, Coderre argued that there should be a public airing of the scientific and medical arguments supporting vaccination. In an open letter to Hingston, dated 8 January 1876, Coderre pressed him to form a commission to investigate the statistical

MONTREAL. ST. GEORGE (MAYOR HINGSTON) AND THE DRAGON (SMALL POX.)

Figure 3.5 William Hales Hingston portrayed as St George slaying the 'smallpox dragon'. Source: *Canada Illustrated News*, **14**, 4 November 1876, cover.

and theoretical case for compulsory vaccination. He argued that the commission should consist of one vaccinator, one anti-vaccinator, and a third member chosen by both physicians to collect and interpret the relevant statistics. If such a commission proved that vaccination was as efficacious as claimed, Coderre declared that he would renounce his anti-vaccination stance. However, if the commission found that the evidence did not support vaccination, then Hingston must abandon compulsory vaccination. Coderre concluded his challenge with the note that if Hingston refused to take up the offer, he would be perceived as conceding the case.[55] Hingston's response was to survey the Montreal medical profession's opinion on the matter. He published a lengthy report in favour of vaccination, attached to which were the signatures of 146 family physicians.[56] This neatly bypassed Coderre's attempt to re-engage the Montreal Medical Society in a public debate over vaccine's efficacy.

By December 1875 Hingston publicly dismissed the Anti-vaccination League's arguments as unscientific, simplistic, obtuse, and uninformed. Armed with the theory of attenuation to explain any anomalous data, and with tools such as the sub-categorization of vaccine scars to qualify vaccination as 'true' or 'false', pro-vaccinationists argued that the prophylactic value of vaccination had been proven without a doubt to all reasonable men. The persistent problem that blocked universal acceptance of vaccination was the poor implementation of the technology – a failure of practice, not principle.

Proponents on both sides of the debate were confident that the collection of better statistics would solve the debate. J.W. Mount claimed that there was already a significant body of proof to support the procedure, but that anti-vaccinationists simply selected from the data anything that supported their arguments.[57] Of course, the same accusation could have been directed at the pro-vaccinationists, who attributed any failure of vaccine to its imperfect practice rather than its principle. Pro-vaccinationists maintained that patients had to be properly vaccinated, then re-vaccinated. If they caught smallpox, the disease would have been more severe had they remained un-vaccinated. Pro-vaccinationists read efficacy into the nineteenth-century data, just as anti-vaccinationists read failure. Hingston was justified in stating that trying to convince someone who did not believe in the principle of vaccination of its efficacy was like trying to convince someone of the reality of a projectile that 'almost' fractured their skull. Anti-vaccinators would likely have agreed with this assessment as it laid bare precisely the kinds of judgements required to assess the technology. The debate over vaccination ended in stalemate, but, as smallpox was on the decline in Montreal, the impetus for compulsion faded away, and so too did the debate over the nature of smallpox and its relation to vaccination.

Conclusions

Moulin has argued that vaccine research in the nineteenth century was almost purely an empirical endeavour, and one that eschewed theory and failed to make any significant breakthroughs in ideas about immunity. This case study suggests otherwise. Not only were physicians struggling to understand immune phenomena associated with vaccination, they were also assigning a natural law that conformed to their experience. As shown, they were heavily influenced by theories of viral attenuation, which provided both a fairly satisfactory explanation for how immunity worked, and explained the variable potency of vaccine. However, measuring the impact of a mutable vaccine on what was

arguably a mutable contagion became increasingly difficult, as statistical data showed an ambiguous picture of vaccine's efficacy. As Rusnock has pointed out, the early part of the nineteenth century was a time when smallpox was ubiquitous and the chances of escaping the disease altogether nearly zero. The issues of the risks of vaccination and the duration of protection were thus overshadowed by the risks of the disease itself. By the 1880s, smallpox was not inevitable, and it was clear that, as then practised, vaccination did not provide permanent protection against the disease – it could even itself spread disease or cause life-threatening infections. It was also clear that not all vaccinations were equal, as many leading pro-vaccinationists were willing to discount a faint or single scar as an index of protection.

When pressed to explain the widespread failure in vaccination, as measured by the complex epidemiology of smallpox among the vaccinated, pro-vaccinationists were drawn to explanations that located the source of the failure in the variable attenuation of vaccine. The commitment to both the principles of vaccination, and the theory of viral attenuation, embedded a theoretical framework into all the epidemiological data constructed in this period to promote vaccination. It also shaped vaccine practices and the selection of stock vaccines, in particular it supported the push to replace Jennerian vaccines with less attenuated, and more potent, animal vaccines. However, the pro-vaccinationists' use of viral attenuation theory under-determined the statistical data leaving the door open for other interpretations.[58] Anti-vaccinationists successfully adapted Jenner's theory of smallpox attenuation to re-interpret clinical data and to provide an opposing but coherent explanation to support their beliefs. The complexity of smallpox aetiology, suggested by attenuation theory, provided them with a sophisticated theoretical framework to explain vaccine injury and failure as the unintended consequences of intervening in the natural life cycle of a disease.

Acknowledgements

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Notes

1 Anne Marie Moulin, 'La métaphore vaccine. De l'inoculation à la vaccinologie', *History and Philosophy of the Life Sciences*, **14**, 1992, pp. 271–97; idem, *Le dernier langage de la medicine: Histoire de l'immunologie de Pasteur au SIDA*, Paris: P.U.F., 1991. Moulin argues that there were no major breakthroughs in the period when 'vaccinology' reigned as a metaphor; there was, she says, no universal theory to explain vaccine-induced immunity, but she ignores that within certain regional contexts, there was significant agreement on the nature of smallpox virus and its relationship to vaccine. Margaret Schibuk and I both question labeling the predominant theory used to explain vaccine's action as metaphorical. Attenuation is better described as a working theory than as a metaphor though Schibuk describes attenuation as a heuristic rather than a coherent theory. See Margaret Schibuk, 'The Search for Vaccinia', PhD

Dissertation, Harvard University, 1986; Jennifer Keelan, 'The Canadian Anti-Vaccination Leagues, 1872–1892', PhD Dissertation, University of Toronto, 2004, chapters 2, 3.

2 Warwick Anderson, Myles Jackson, and Barbara Guttman Rosenkrantz, 'Toward an unnatural history of vaccination', *Journal of the History of Biology*, **27**, 1994, pp. 575–94. Their example is the intellectual dead-end, as they see it, of natural or racial immunities (p. 582), which were jettisoned from the research programme of the histories of immunology, bacteriology, and serology, as these became autonomous disciplines.

3 Edward Jenner, *An inquiry into the causes and effects of the variolae vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of the cow pox*, London: Sampson Low, 1798.

4 Sanjoy Bhattacharya, Mark Harrison, and Michael Worboys, *Fractured States: Smallpox, Public Health, and Vaccination in British India*, Delhi: Orient Longman Private Limited, 2005; Nadja Durbach, *Bodily Matters: The Anti-vaccination Movement in England 1853–1907*, Durham and London: Duke University Press, 2005.

5 'Not a Catholic Dog', *New York Times*, 24 September 1876, p. 2.

6 A.B. LaRocque, *Annual Report of the Medical Officers of Health of the City of Montreal for the Year 1876*, Montreal: Louis Perrault & Co., City Printers, 1876, pp. 16–18, 38–48, Montreal City Archives (hereafter MCA). See also, 'Vaccination in Montreal', *Canada Medical Record*, **3**, 1874, p. 569.

7 Montreal was a city of roughly 100,000 people in 1872, when 897 deaths from smallpox were recorded. Mortality from smallpox varied from year to year, with 228 deaths in 1873, 704 in 1876, and 728 in 1878. By 1880 there were only 104 deaths from smallpox and the rate dropped off quickly until the epidemic of 1885. According to the Annual Report for 1876 (n. 6), around 72% of the recorded deaths from smallpox in 1873 were of children under five years of age. For a discussion of how poor vaccination practices led to anti-vaccinationism see, 'Vaccination – Its protective power', *The Canada Lancet*, **8,** 1875, p. 57.

8 'The Anti-vaccination Movement', *The Canada Lancet*, **1**, 1872, p. 134. In the annual report of the medical officers for 1875 the total mortality in the French Canadian population was 40.48 per thousand, in the Irish Catholic population 18.60 per thousand and in the English Protestant population, 18.17 per thousand. This was compared with a variety of European cities whose annual mortality rates ranged from 22.5 per thousand (London) to 34.3 (Rome) and to American cities 19.2 (San Francisco) and New Orleans (32.8). *Report of the Medical Officers of Health of the City of Montreal for the Year Ending December 1875*, Montreal: Louis Perrault & Co., City Printers, p. 7, MCA. For a discussion of the impact of smallpox in raising overall mortality see pages 11–12 of the same report.

9 Moulin, 'La métaphore vaccine' (n. 1).

10 Michael Farley, Peter Keating and Othmar Keel, 'La vaccination à Montréal dans le seconde moitié du 19e siècle: Pratiques, obstacles et resistances', in Michael Fournier, Yves Gingras and Othmar Keel, *Science et medicine au Québec: Perspectives Sociohistoriques*, Montreal: Institut québecois de recherche sur la culture, 1987.

11 Schibuk, 'The Search for Vaccinia' (n. 1).

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13 For an example, see Joseph Emery Coderre, *Vaccination Étude lue à la Société médicale de Montréal, les 31 janvier, 14 & 28 février 1872*, Montreal, 1872.

14 Angelo Gatti, *Réflexions sur les préjugés qui s'opposent aux progress et à la perfection de l'inoculation*, Bruxelles, Musier, 1764. Trans. by Genevieve Miller, quoted in C. Huygelen, 'The Concept of Viral Attenuation in the Eighteenth and Nineteenth Centuries', *Biologicals*, **25,** 1997, p. 339.

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16 Ibid., p. 88.

17 Schibuk, 'Search for Vaccinia' (n. 1)

18 Ibid., pp. 84–110.

19 John Badcock, *A Detail of Experiments Confirming the Power of Cow Pox to Protect the Constitution from a Subsequent Attack of Small Pox by Proving the Identity of the Two Diseases*, Brighton: King, 1845; Robert Ceely, 'Observations of the Variola Vaccine', *Transactions of the Provincial Medical and Surgical Association*, **8**, 1840, pp. 287–435. These two were the most often cited. The French researcher M. DePaul became a vocal advocate of this 'unicist' theory though there was a strong 'dualist' camp in France led by A. Chauveau. See M. DePaul, *De l'origine réelle du virus vaccin*, Paris: Ballière, 1864; for Chauveau's critical dualist experiment, see A. Chauveau, *Vaccine et variole. Nouvelle étude experimentale sur la question de l'identité de ces deux affections*, Paris: Asselin, 1865.

20 Schibuk, *The Search for Vaccinia* (n. 1). For Montreal see n. 16.

21 William Osler, *The Principles and Practice of Medicine: Designed for the Use of Practitioners and Students of Medicine*, third ed., New York: Appleton, 1899, p. 70.

22 Ceely, 'Observations of the variola vaccine' (n. 19); analyzed in Edgar March Crookshank, *History and Pathology of Vaccination Volume 1,* London: H.K. Lewis, pp. 363–469. Many medical texts between 1860 and 1900 refer to Ceely's work as having been confirmed by other studies.

23 P.E. Plante, 'Société Médicale de Montréal: Séance du 20 decembre 1871', *L'Union médicale du Canada*, **1**, 1872, p. 133. Dr Plante reported that he had worked at the *Hôtel Dieu* for years, attending hundreds of cases of smallpox, without ever being vaccinated.

24 William H. Hingston, *Remarques sur la vaccination'*, Montreal, 1876, p. 16.

25 Andrea Rusnock, *Vital Accounts*: *Quantifying Health and Population in Eighteenth-Century England and France*, Cambridge University Press, 2002.

26 George Wright, 'Vaccination – its efficacy,' *Canadian Journal of Medical Sciences*, **1,** 1876, p. 59.

27 As was noted in the annual report for 1876, of the 97 deaths from smallpox in the Civic Hospital, 75 were not vaccinated, 19 were insufficiently vaccinated 'there being only one vaccine mark on each and on the greater number of these the mark was almost indistinct, the remaining 3 deaths of persons successfully vaccinated were due mainly to lung complications – pnuemonia and pleura pneumonia'. However about 72 per cent of the total were under five years of age, and about 83 per cent were French Canadians, LaRocque, *Annual Report*, p. 13 (n. 6).

28 Louis LaBerge, *Report on the Sanitary State of the City of Montreal for the Year 1885*, Montreal: Perrault Printing Co., 1886, pp. 22–43, MCA. It is important to note that while reports of un-vaccinated admissions to Montreal smallpox hospitals between 1874 and 1885 ranged between 17 per cent (1883) and 60 per cent (1875) of total admissions, the number of doubtful vaccinations was lumped together with those whose vaccination status was 'unrecorded'. This made the statistics virtually meaningless though they were open to endless interpretation by both pro- and anti-vaccinationists. It is fair to say that the ratio of unvaccinated smallpox patients to confirmed (or properly vaccinated) patients was generally 2:1 but without any way

of separating out the doubtful vaccines from the unknown in the remainder, it was impossible to assess the effect of vaccination without imposing contentious interpretations. The number of doubtful or un-recorded vaccinations in the annual smallpox returns actually increased over time and ranged from 32 per cent in 1879 to 75 per cent in 1883. A summary of the 1874 data is found in *Canada Medical Journal*, **4**, 1875, pp. 161–2.

29 J.E.B. Denarp-Decanteleu, *Monographie des cicatrices de la vaccine: ouvrage dans lequel on fait connaître: Plusiers formes de cicatrices vaccinales non encore décrites: Le monde de formation, les transformations diverses, les caractères des cicatrices que la vaccine peut produire: accompagné d'un tableau iconographie contenant 112 figures disposes méthodiquement*, Paris: J.E. Baillière, 1851. Republished and distributed in America as an appendix to Henry Austin Martin, *On Animal Vaccination*, Boston, 1878.

30 Martin, *On Animal Vaccination*, (n. 29).

31 J.F. Marson, 'Smallpox', in Reynolds (ed.), *System of Medicine*, v. 1, London: Macmillan, 1876, p. 264.

32 Ibid., p. 240.

33 Ibid., p. 261.

34 L.A. Fortier, 'Honneur au Canada! La France ne nous oublie pas', *Le Monde Illustré*, **4**, no. 191, 1887, p. 277.

35 Ibid.

36 A.T. Brosseau, 'Société médicale de Montréal: Séance du 20 décembre 1871', *L'Union médicale du Canada*, **1**, 1872, p. 134.

37 Ibid., p. 132.,

38 L.A.E. Desjardins, 'Société médicale', (n. 36) p. 134. All translations are my own unless otherwise noted.

39 G. Grenier in Brosseau, 'Société médicale' (n. 36), p. 135.

40 P.E. Plante in Brosseau, 'Société médicale' (n. 36), p. 132.

41 Ibid., p. 135.

42 Ibid., p. 133.

43 For the chief supporters of animal vaccination see Martin, *Animal Vaccination* (n. 29) and Bessey, 'Animal Vaccination' (n. 15). For more critical reports see 'Animal Vaccination', *Canada Medical Record*, **5**, 1875, p. 249.

44 Coderre, *Vaccination: Étude lue à la Société médicale de Montréal* (n. 13).

45 Ibid., p. 4.

46 Ibid., p. 8.

47 Ibid., p. 5.

48 Ibid., p. 12.

49 Ibid.

50 Ibid., p. 13.

51 Ibid., p. 20.

52 Ibid., p.13.

53 Alan Hustak, *Sir William Hales Hingston: Montreal Mayor, Surgeon and Banker*, Montreal: Price Patterson Ltd., 2004.

54 William H. Hingston, *Remarks on Vaccination*. Montreal, 1876; idem, *Lecture on Vaccination Delivered on 20th October, to the Public Vaccinators and other invited Physicians and Citizens*, Montreal, 1876. This was re-printed from his article in *Public Health Magazine*. For a description of Coderre's anti-vaccination pamphleteering and his photos of vaccine injured children see Keelan, 'The Canadian Anti-vaccination Leagues', chapter 3, (n. 1).

55 Joseph Emery Coderre to Maire W.H. Hingston, letter d. 8 January 1876, Concordia University Archives, Hingston Family Fonds, P134/A2 Political Career, Box HA 1725.

56 William H. Hingston, 'Instructions aux vaccinateurs', *L'Union médicale du Canada*, **4**, 1876, pp. 1–39 Appendix.

57 J.W. Mount, 'Vaccination: Lettre au Dr A. Dagenais, *L'Union médicale du Canada*, **4**, 1876, pp. 114.

58 For an excellent description of the under-determination of medical theory by statistics see, Gérard Jorland, 'La sous-détermination des theories médicales par les statistiques: Le cas Semmelweis', in G. Jorland, A. Opinel and G. Weisz (eds), *Body Counts: Medical Quantification in Historical and Sociological Perspectives*, McGill-Queen's University Press, 2005, pp. 205–25. For a detailed discussion of anti-vaccination statistical analyses see, Jennifer Keelan and Martin Fichman, 'Resister's Logic: The Anti-vaccination Arguments of Alfred Russel Wallace and Their Role in the Debates over Compulsory Vaccination in England, 1870–1907', *Studies in History and Philosophy of Biological and Biomedical Sciences* (in press).

PART II
The Conundrum of Allergy

CHAPTER FOUR

'A Private Line to Medicine': The Clinical and Laboratory Contours of Allergy in the Early Twentieth Century

Mark Jackson

Introduction

In 1976, the Nobel Prize winning Danish immunologist Niels Jerne (1911–94) began his introduction of an expansive collection of papers on the origins of lymphocyte diversity at the Cold Spring Harbor Symposium on Quantitative Biology by reviewing what he termed 'the common sense of immunology', that is, the range of immunological 'notions that have gained general acceptance' by immunologists at any one time. After exploring discussions from a previous symposium on antibodies in 1967 that had vindicated the clonal selection theory proposed by Frank Macfarlane Burnet (1899–1985), and then outlining the nature of current debates about lymphocyte structure and function, Jerne looked to the future. Recognizing the progress that had been made since immunology's origins in the late nineteenth century, he highlighted the potential for basic immunological research to 'lead to important medical advances'. In the process, he implied that the development of closer links between the immunological bench and the bedside had been, and would continue to be, made possible by the persistent clinical orientation of certain sub-disciplines within immunology:

> Immunology has come a long way. It used to be an esoteric subject employing its own terminology (immunity, sensitivity, tolerance, avidity, etc.) to deal with problems that seemed scarcely related to other fields of biology. Because of vaccination, allergy and serological diagnosis, immunology had a private line to medicine, which compensated for its isolation.[1]

Jerne's evaluation of the distance that had separated many laboratory immunologists from their colleagues in the biological sciences and in the clinic during the first half of the twentieth century and his explicit attempts to bridge that gap are instructive. As Jerne's reflections elsewhere demonstrate – and as many historians of immunology have pointed out – the 1960s and 1970s constituted a critical moment in the emergence of a 'new immunology'.[2] Not only were stronger links promoted between immunobiologists and immunochemists (or what Jerne referred to as cis- and trans-immunologists), but immunologists also became anxious to prioritize and publicize the biological

tenor and clinical significance of their research. Although Jerne acknowledged that immunochemical approaches had clearly elucidated many critical features of antibody structure, he suggested that by the 1960s 'the wrinkled features of immunology were definitely in need of a face-lifting'.[3] Within this context, Jerne's appropriation of allergy, serology and vaccination into the immunological fold served not merely to emphasize the clinical tradition within immunology; it also facilitated and endorsed a fundamental intellectual and political transformation in the discipline.

As Warwick Anderson, Myles Jackson, and Barbara Gutmann Rosenkrantz warned some years ago, however, historians should be wary of accepting without question the retrospective constructions of the history of immunology by leading immunologists, since they often served discrete professional purposes.[4] Indeed, there is some contemporary evidence to challenge Jerne's surreptitious affirmation of a close and unproblematic link between allergy and immunology during the twentieth century. According to Lucia Fisher-Pap, who surveyed the relative positions of immunology and allergy in 1975, for example, not only was the relationship between the two disciplines more often 'a marriage of convenience' than a 'wedding of love', but allergists also occupied largely separate professional spaces both from other clinical specialists and from most laboratory immunologists.[5] Similarly, some historians have suggested that during the early twentieth century immunologists were troubled by the paradoxes of immunologically-mediated diseases and deliberately turned away from studies of allergy and anaphylaxis, leaving allergists on the fringes of the field. Such assertions have been tentatively supported by prosopographical evidence demonstrating that, although the origins of immunology and allergy were both rooted in the explosion of biological and pathological sciences in the late nineteenth century, there was in reality little overlap between the two areas for much of the twentieth century. According to Arthur Silverstein and Thomas Söderqvist, for example, allergists only 'rarely attended other immunological meetings' at least until the 1970s and allergy conferences and symposia 'did not contribute substantially, if at all, to the integration of clinical and basic theoretical issues in immunology'.[6]

Both Jerne's reconstruction of disciplinary relations between allergy, immunology and medicine, and contemporary and historical objections to that reconstruction, raise significant questions about the intersecting histories of immunology and allergy that this chapter aims to explore. In the first place, the history of allergy, implicit in these accounts, challenges traditional narratives of the evolution of immunological theories and practice. According to many historical accounts, during the nineteenth and twentieth centuries, immunological approaches to bodily defence mechanisms and disease were framed by a series of distinct paradigm shifts.[7] During immunology's infancy between approximately 1880 and 1910, both laboratory and clinical immunology were closely allied to experimental pathology and physiology. This linkage served to encourage the development and dissemination of immunological treatments for infectious diseases, such as vaccination (the use of vaccines to stimulate prophylactic active immunity), vaccine therapy (the use of vaccines to cure on-going bacterial infections), and serotherapy (the administration of antisera to confer passive immunity).

During the early twentieth century, by contrast, declining support for vaccine therapy,[8] together with the advent of 'immunochemistry' (a term introduced by the Nobel Prize winning Swedish chemist Svante Arrhenius in 1904),[9] served to divorce immunology from physiology and pathology and to divert immunological attention away

from clinical problems towards more detailed laboratory studies of the biochemistry of antibodies and antigens. During this period, in which a 'tyrannical chemical view [was] imposed upon studies in immunity',[10] the 'zone of collaboration'[11] between clinicians and scientists was effectively reduced. As Ilana Löwy has suggested, although the loss of interest in cellular phenomena was not complete, as a result of the 'immunochemical turn', immunology became 'a set of esoteric laboratory practices isolated from the mainstream of biological knowledge'.[12]

After the Second World War, however, a further transition was effected. A revival of interest in immunobiological phenomena, such as transplant rejection, tumour biology, autoimmune diseases, and, to some extent, allergies, apparently provided the momentum for the emergence of a 'new immunology', in which cellular mechanisms once again took centre stage amidst debates about the ability of organisms to distinguish 'self' from 'non-self'. This process in turn allowed 'the development – or rather the reconstitution – of a "zone of collaboration" between scientists and physicians interested in immunology'.[13] As Jerne insisted in the 1970s and as several historians have subsequently agreed, immunology thus became a specialty which once again linked 'fundamental biological research with medical practice'.[14]

Significantly, this tri-phasic history of immunology does not fit the intellectual evolution and disciplinary direction of allergy studies in the early twentieth century. Indeed, the origins and emergence of allergy as a specialty offer several interesting counterpoints to the general historical narrative in which immunology became temporarily divorced from the exigencies of clinical medicine in that period. This is not to say that laboratory experimental work was not important in fashioning early understandings of allergic reactions. On the contrary, at the start of the twentieth century, a number of crucial experimental observations in both humans and animals provided the basis for the elaboration of new immunological models of disease. Novel clinical understandings of pathogenesis were thus informed by the work of Charles Richet (1850–1935) and Paul Portier (1866–1962) on anaphylaxis, by subsequent investigations of the specific biological mechanisms and manifestations of anaphylactic sensitization by Maurice Arthus (1862–1945), Milton Rosenau (1869–1946), and John Anderson (1873–1958), and by the studies of histamine carried out by Henry Dale (1875–1968) and his colleagues at the Wellcome Physiological Research Laboratories.[15] However, as I shall argue in this chapter, while research in the field of experimental physiology provided a preliminary framework for exploring and explaining allergic reactions, early formulations of allergy and the subsequent development of the field on both sides of the Atlantic were shaped more precisely by encounters with patients in the clinic. In many ways, as Jerne intimated, allergists (perhaps alone amongst students of immunological processes) refused to relinquish the 'zone of collaboration' between the bench and the bedside.

In addition to challenging broad interpretations of the history of immunology, the history of allergy also raises questions about the scope of the 'laboratory revolution' in medicine. According to Andrew Cunningham and Perry Williams, in their expansive edited volume analysing the rise of laboratory medicine, 'modern medicine is based in the laboratory'. As a result of dramatic developments in the biomedical sciences, in medical education, and in the political regulation of the medical profession during the nineteenth century, it was both the experience and the knowledge gained from observations in the laboratory (rather than those made in the hospital or at the bedside)

which came to 'provide the power and authority of modern medicine'.[16] In some ways, the immunochemical turn within immunology supports this interpretation of the gradual dominance of the laboratory. However, as I shall suggest here, while leading allergists such as John Freeman (1876–1962) undoubtedly recognized the value of laboratory research and frequently emphasized the symbiotic nature of the relationship between laboratory and clinic, the study of allergy during the first half of the twentieth century revolved almost exclusively around clinical practice.[17]

Reservations about the relevance of broad histories of immunology and the laboratory to the history of allergy raise a final, and perhaps more fundamental, question about the relationship between allergy and immunity, and by inference the relationship between allergy and immunology, during the early twentieth century. When Clemens von Pirquet (1874–1928) introduced the term allergy in 1906, he regarded allergy as a convenient umbrella term for all forms of altered biological reactivity including both immunity and hypersensitivity. For von Pirquet, immunity and hypersensitivity constituted opposite sides of the same immunological coin.[18] However, von Pirquet's formulation of allergy was rapidly abandoned. Frustrated by the contradictions inherent in the notion of immunologically-mediated diseases, immunologists regarded allergy (or hypersensitivity) largely as an aberration or anomaly and diverted their attention to elucidating the biochemical mechanisms of bodily defence (or immunity).[19] By contrast, allergists concentrated predominantly on understanding and treating the clinical manifestations of hypersensitivity and ignored experimental studies of immunological processes. In this way, a fundamental chasm was established not only between theoretical formulations of 'allergy' and 'immunity' but also between the disciplinary trajectories of allergy and immunology. In spite of Jerne's retrospective attempt to incorporate allergy into the immunological fold, it may well be that the growth of allergy and immunology during the first half of the twentieth century should be regarded as discrete, rather than overlapping, phenomena. Indeed, this disciplinary fissure may well explain why historians of immunology have, until recently, been reluctant to pursue what Anderson, Jackson and Rosenkrantz have referred to as the rather more 'vague and contingent' history of allergy.[20]

This chapter aims to explore such questions by tracing the origins and expansion of allergy studies on both sides of the Atlantic during the first half of the twentieth century. By focusing particularly on the work of von Pirquet and Freeman, the manner in which allergists, unlike immunologists, developed and maintained loose but effective links between the clinic and the laboratory in this period can be elucidated. However, although the origins of allergy were deeply rooted in both clinical and experimental studies and although close connections between work at the bench and the bedside remained central to the evolution of allergy and to the self-image and professional identity of modern allergists, I shall argue that allergy emerged predominantly as a clinical specialty relatively untouched by the tyranny of immunochemistry or by the laboratory revolution. In the process, I shall attempt to evaluate in a preliminary manner the suggestion implicit in Jerne's words that the persistent clinical orientation of allergy facilitated the effective re-integration of immunology and medicine in the 1950s and 1960s.

The Origins of Allergy

The notion of allergy as an immunological phenomenon with significant clinical manifestations was initially conceived by von Pirquet while he was working in the paediatric wards in Vienna. The son of an aristocratic Belgian father and a Viennese mother, von Pirquet took a degree in theology before entering medicine, largely against the wishes of his family. Having studied in Vienna, Königsberg, and Graz, where he gained his MD in 1900, he spent six months as a medical officer in the armed forces and then chose to specialize in paediatrics, working first in Berlin under Otto von Heubner before beginning his internship and residency in 1901 at the *Universitäts Kinderklinik* in Vienna. Apart from a brief period in North America, where he became the first professor of paediatrics at Johns Hopkins University in Baltimore, and a short time at the University of Breslau in Germany, von Pirquet spent the whole of his professional life in Vienna, eventually succeeding his mentor, Theodor Escherich, as professor of paediatrics at the new *Kinderklinik* in 1910.[21]

From the outset of his career, von Pirquet developed a close interest in a variety of immunological problems, publishing early papers on specific precipitation, serum sickness, and the agglutination of streptococci.[22] It was the study of incubation times in acute infections, vaccinations, and serum sickness, however, which provided the foundation for many of his later reflections in, and contributions to, the field. The idea to focus on incubation times had apparently been proposed by Max Gruber (1835–1927), professor of hygiene at the Universities of Vienna and Munich, who had suggested to von Pirquet that 'a study of incubation time would furnish an important clue to the concept of immunity'.[23] In addition, von Pirquet's interest in charting the development of immune responses through time may well have been influenced by contemporary preoccupations amongst paediatricians both in Europe and North America with accurately recording and analysing the fundamental features, or milestones, of child development.[24]

Von Pirquet's initial speculations about the significance of incubation times focused on the natural history of childhood diseases and vaccination reactions, and on the character of antigen-antibody interactions. Together with Gruber, for example, von Pirquet participated in frequently hostile debates about antibody-antigen interactions by publishing articles which challenged Paul Ehrlich's account of the neutralization of toxin by antitoxin.[25] More critically in the present context, however, von Pirquet's reflections on incubation times led him to question traditional views of the role of micro-organisms and their toxins in human disease. In 1903, in a preliminary paper on the theory of infectious diseases, he argued that the cardinal signs of illness (fever, exanthemata, a decrease in white cells in the blood, and other constitutional symptoms) were dependent not solely on the action of the invading bacteria but also on the body's ability to develop antibodies which subsequently reacted with those bacteria and their toxins:

> 1. The length of the incubation time depends not only upon the foreign body, but also upon the organism in question.
> 2. The manifestations of disease appear at the moment when the antibodies formed in the organism begin to react with the causative foreign body.

> 3. The acquired immunity, which persists, lies in the ability of the organism to produce the antibodies more rapidly than before, and there is a corresponding shortening of incubation time.[26]

Von Pirquet's belief that specific biological responses, as well as external agents, were primarily responsible for clinical symptoms was contrary to mainstream pathological approaches at that time. While clinicians and pathologists certainly understood pathogenesis in temporal terms, they generally construed the signs of disease simply as the product of the invasion of a host by a hostile organism. From this perspective, the subsequent course of disease was visualized in terms of a battle between external aggressors (bacteria and their toxins) causing tissue damage and internal defence mechanisms (white blood cells and antibodies). However, although it represented a departure from the dominant paradigm, von Pirquet's formulation of the pathogenesis of acute infectious diseases and vaccination reactions, in which the body itself played a critical role, was not entirely new. As Ohad Parnes and Löwy have recently suggested, around the turn of the century a number of clinicians and scientists, such as Carl Weigert (1845–1904), Tytus Chalubinski (1820–1889), and Ludwik Fleck (1896–1961), also understood pathology in more dynamic and holistic terms, stressing the contribution of host reactions to the manifestations of disease.[27]

Faced by the clinical challenge of treating patients in the paediatric wards in Vienna, von Pirquet subsequently extended his observations on the natural history of infectious diseases and vaccination reactions to the study of serum sickness, in which children treated with antisera developed severe systemic reactions including fevers, rashes, diarrhoea, falling blood pressure, joint pains, breathing difficulties, and sometimes death. Focusing once again on the temporal characteristics of the clinical phenomena, von Pirquet and his Hungarian co-worker, Béla Schick (1877–1967), demonstrated that serum sickness presented a familiar set of pathological features. In particular, clinical experience confirmed that the onset of symptoms after serum therapy followed a pattern analogous to that exhibited in infectious diseases: there was a reproducible interval, or incubation period, between the initial injection and the appearance of symptoms; and subsequent injections (like secondary exposure to infection) were accompanied by accelerated and exaggerated responses. Von Pirquet and Schick concluded that the clinical features of serum sickness were not the direct product of the antiserum but the outcome of a hypersensitivity reaction characterized by 'a collision of antigen and antibody'. The results of their investigations into the role of host reactivity in the pathogenesis of serum sickness, first tentatively announced in 1903,[28] were subsequently expounded in a seminal book published in 1905:

> The conception that the antibodies, which should protect against disease, are also responsible for the disease, sounds at first absurd. This has as its basis the fact that we are accustomed to see in disease only harm done to the organism and to see in the antibodies solely antitoxic substances. One forgets too easily that the disease represents only a stage in the development of immunity, and that the organism often attains the advantage of immunity only by means of disease.[29]

It was these distinct but related observations of clinical phenomena gleaned from the bedside that provided von Pirquet with both the evidence and the impetus to formulate

the concept of allergy. In a brief (now classic) paper published in the *Münchener Medizinische Wochenschrift* in 1906, von Pirquet proposed an elegant description of immunological reactivity, in which he attempted to account for similarities in the natural histories of serum sickness, infectious diseases, and vaccination reactions, and to reconcile the apparent contrast between immunity and hypersensitivity. Although von Pirquet acknowledged that the 'two terms contradict each other', he nevertheless emphasized close biological parallels between immunity and hypersensitivity, particularly in terms of the shifting chronology of the response on primary and secondary exposure to antigen. Anxious to synthesize existing knowledge and to facilitate further research in this area, he proposed the introduction of a new general term which would express 'the change in condition which an animal experiences after contact with any organic poison, be it animate or inanimate':

> For this general concept of a changed reactivity I propose the term allergy … The vaccinated, the tuberculous, the individual injected with serum becomes allergic towards the corresponding foreign substance … The term immunity must be restricted to those processes in which the introduction of the foreign substance into the organism causes no clinically evident reaction, where, therefore, complete insensitivity exists.[30]

Von Pirquet immediately recognized the clinical implications of his approach to altered reactivity. In particular, he explicitly linked his novel formulation of immunological reactivity, or allergy, to traditional clinical notions of idiosyncrasy, thereby paving the way for new understandings of a range of both well-established and seemingly novel conditions.

> Among the allergens should be included the poisons of mosquitoes and bees in so far as their stings are followed by hypo- or hypersensitivity. For this reason we may also enrol under this term the pollen causing hay fever (Wolff-Eisner), the urticaria-producing substances of strawberries and crabs, and probably too a number of organic substances leading to idiosyncrasy.[31]

Although von Pirquet drew predominantly on his own clinical experience to formulate the concept of allergy and although his attention was largely concentrated on the clinical implications of his ideas, he was also keen to incorporate into his theory of altered reactivity the disparate observations of hypersensitivity reported by experimental physiologists studying the reactions of various animals to the injection of foreign substances. In his 1906 paper, for example, he cited the work of Emil von Behring on the signs of supersensitivity (*überempfindlichkeit*) in guinea pigs exposed to repeated doses of diphtheria toxin, the seminal laboratory studies of Richet and Portier on anaphylactic reactions in dogs, and the research of Rosenau and Anderson illustrating the supersensitivity of guinea pigs to horse serum.[32] His awareness of the experimental laboratory tradition which had made the notion of allergy possible is also evident in his reflective overview of the history of allergy published in 1927, shortly before his death; although the majority of the paper focused on his own contributions to the field, he opened his discussion by referring at length to the laboratory studies of Richet, Arthus, and Theobald Smith.[33]

In 1911, von Pirquet published a more expansive account of immunological reactivity and disease, in which he developed many of the ideas that he had sketched out only in skeleton form in 1906.[34] The 1911 monograph illustrates, in the first place, the manner in which he clearly retained a close interest in the seemingly paradoxical relationship between immunity and hypersensitivity. Secondly, his focus remained steadfastly fixed on tracing the precise temporal, qualitative and quantitative aspects of various types of altered reactivity that enabled him to compare and contrast diverse clinical and laboratory observations of hypersensitivity reactions. Finally, he retained his strong emphasis on the broad clinical significance of allergy. Although much of the text was preoccupied with serum sickness and vaccination reactions in humans and with experimental anaphylaxis in animals as paradigmatic forms of allergy, von Pirquet also considered the role of altered immunological reactivity in urticaria, food idiosyncrasies, and hay fever, and speculated about the contribution of allergy to the symptomatology of various infectious diseases, such as syphilis, scarlet fever, and tuberculosis. Indeed, his clinical preoccupations are betrayed by his insistence on using the word allergy primarily as 'a clinical conception without being prejudiced by the bacteriological, pathological or biological findings'.[35]

In his 1911 monograph, von Pirquet also reflected more extensively on the possible mechanisms involved in the pathogenesis of these conditions, drawing both on his own clinical observations at the bedside and on his reading of the results of experimental work in animals. In particular, he reviewed contemporary disputes about the nature of the sensitizing substance (or allergen), summarized evidence regarding the specificity of 'serum allergy', and discussed the results of experiments demonstrating the passive transfer of anaphylaxis. Although the precise character and mode of action of the serum factors responsible remained unknown, von Pirquet was convinced that most forms of allergy (whether leading to immunity or hypersensitivity) were mediated by antibodies interacting in some way with an allergen. The implications of this hypothesis, which closely echoed his own earlier reflections on the pathogenetic significance of host reactivity, were not lost on von Pirquet:

> This explanation involved also quite a new conception of an antibody. Thus far the antibodies were numbered among the protective substances, which is just the contrary of the supposition. Diphtheria antitoxin was considered as a typical antibody. The action of this antibody is to neutralize completely the antigen, i.e., the diphtheria toxin, while in my hypothesis these other antibodies form a new toxic body with the antigen. The principal new conception consisted in the suggestion that a disease might be due indirectly to an antibody, an idea to which at that time adherents of the school of Ehrlich, like Kraus, took strong exception.[36]

As von Pirquet's words imply, his approach to immunity and hypersensitivity was not well-received by many of his contemporaries. In particular, critics dismissed his terminology, his emphasis on host reactivity in human disease, and his insistence on the close parallels between immunity and hypersensitivity. In promoting his own understanding of the precise mechanisms operating in anaphylaxis, for example, Richet condemned the introduction of what he regarded as an unnecessary new term: 'Pirquet and Schick have termed the reaction of an organism to a foreign substance *allergy*; but it does not appear necessary to me to introduce this word in addition to the word

anaphylaxis'.[37] Richet's rejection of the term allergy was echoed elsewhere. When von Pirquet's book was reviewed in the *Lancet* in 1911, the reviewer referred to the term as 'not a happy combination', and pointed out that Richet had already coined the word anaphylaxis for increased sensitivity.[38] Some years later, in their preliminary classification of the phenomena of hypersensitivity, Arthur F. Coca (1875–1959) and Robert A. Cooke (1880–1960), two leading American immunologists, also expressed their dissatisfaction with the word 'allergy' as a means of classifying even clinical conditions, since adherence to von Pirquet's original definition resulted in the inclusion of diseases 'of such different nature as to make their association valueless if not positively confusing'. In its place, Coca and Cooke advocated simply using the term hypersensitivity, which, as they explained, was already in regular use in the literature on anaphylaxis.[39]

Contemporary commentators also challenged von Pirquet's account of serum sickness and his emphasis on the role of antibodies in the pathogenesis of human diseases. In a short study of immune sera published in 1908, Charles Bolduan (b. 1873), a German-born bacteriologist working in New York, discussed experiments in guinea pigs which, he argued, indicated that von Pirquet and Schick's theory that serum disease was the direct product of an interaction between antigen and antibody was 'untenable'.[40] Coca and Cooke also disputed von Pirquet's explanation of the features of serum sickness. In particular, they cited studies which had failed to demonstrate any correlation between the symptoms of the disease and the presence or absence of either 'specific precipitins' or 'antigen' in the blood. Arguing that this lack of relationship alone was 'sufficient to overthrow von Pirquet's theory', Coca and Cooke insisted that serum disease in humans was not directly comparable to anaphylaxis in animals, as von Pirquet's work had implied.[41] In doing so, they not only rejected the explicit link that von Pirquet had constructed between immunity and hypersensitivity but also, as Jules Bordet (1870–1961) had done before them, disputed the clinical significance of laboratory demonstrations of anaphylaxis.[42]

Von Pirquet periodically responded to criticism by carefully evaluating competing theories of hypersensitivity. In his 1911 monograph, for example, he pointed out that Richet's belief that immunity and hypersensitivity, to a particular poison, were stimulated by 'two different substances' remained speculative, since 'thus far the separate existence of both these hypothetical substances has not been proved'.[43] However, von Pirquet was acutely aware that his work on the analogies between serum sickness, vaccination and infectious diseases 'remained unnoticed', and that 'the main point of the theory, the difference in the time of reaction, has not been understood by many scientists'.[44] Von Pirquet's assessment appears to have been accurate. While the notion of allergy, and more specifically the role of host reactivity, remained marginal to many studies in experimental physiology and clinical pathology, interest in anaphylaxis by contrast blossomed. During the first two decades of the twentieth century, an expanding stream of articles and books on anaphylaxis (rather than allergy) appeared in a number of languages.[45] In addition, contemporary commentators both in Europe and in North America noted, sometimes ironically, how anaphylaxis had become 'one of the most popular scientific terms of the day'.[46]

Significantly, however, while anaphylaxis proved immediately popular, von Pirquet's formulation of allergy gradually attracted increasing attention and support from clinicians and scientists. It is noticeable, for example, that when Richet was awarded the Nobel Prize in 1913 for his experimental work on anaphylaxis, the linguistic and scientific tides

were perhaps already beginning to turn. The previous year, the American pathologist Ludvig Hektoen (1863–1951) had published an article in the *Journal of the American Medical Association* in which he not only used the terms anaphylaxis and allergy almost interchangeably but also made explicit the links between the laboratory and the clinic that had been central to von Pirquet's formulation of the concept of altered reactivity.[47] Four years later, in an article in the *Lancet* on prophylactic vaccination against hay fever, B.P. Sormani, a lecturer in serology in Amsterdam, similarly used allergy as a shorthand for 'hypersensibility for the pollen extract'.[48] By the late 1920s, the titles of a number of books and journal articles, as well as the emergence of 'allergy clinics' around Europe and North America, suggest that the concept of allergy was slowly superseding anaphylaxis as a means of not only describing, but also conceptualizing and analysing, a variety of experimental and clinical phenomena within what von Pirquet referred to as 'the domain of Immunology'.[49]

The construction of a new conceptual framework was not the only legacy of von Pirquet's formulation of altered reactivity. Always alert to the clinical implications of his findings, von Pirquet's studies led him to suggest that modified skin reactions to bacteria or their toxins might be utilized for diagnostic purposes. Applying his observations to tuberculosis, he suggested in 1907 that the nature of the skin reaction to inoculation with tuberculin (or 'the tuberculin test') could be used to determine whether or not a patient had been in contact with the tubercle bacillus. Although the test could not necessarily distinguish between old and active infection (especially in adult patients), von Pirquet was insistent not only that the cutaneous test was preferable to the conjunctival test later introduced by Albert Calmette (1863–1933) but also that the test was important in prevention, since it could reveal which children in hospitals and schools were tuberculous and should therefore be segregated.[50] Von Pirquet was manifestly proud of what he termed 'the allergy test' for tuberculosis. As he pointed out in a review of the field of allergy, published in 1927, his 'finding of most practical importance, the cutaneous tuberculin reaction, is used by paediatricians all over the world with the same interpretation I devised years ago'.[51] Although there were recurrent debates about the precise role and the nature of hypersensitivity in the evolution of immunity against tuberculosis during the middle decades of the twentieth century, von Pirquet's test (as it became more commonly known) became a standard diagnostic tool and served as the model for the development of similar tests for other diseases, such as diphtheria, glanders, and actinomycosis.

Von Pirquet's notion of allergy carried other consequences. By postulating a clear link between immunity and hypersensitivity, von Pirquet helped to maintain interest in the role of what were generally regarded as the body's defence mechanisms in dictating the symptoms and course of human diseases. Whether framed primarily in terms of hypersensitivity, anaphylaxis, or allergy, altered immunological reactivity was rapidly implicated in the pathogenesis of a number of conditions increasingly referred to as 'allergic disorders': hay fever; asthma; urticaria and eczema; food idiosyncrasies; supersensitivity to aspirin and other drugs; reactions to bee stings; infectious diseases, in particular tuberculosis; and a variety of diffuse clinical manifestations such as rheumatism, eclampsia, migraine, and epilepsy. By drawing together a range of disparate clinical conditions in this way, von Pirquet's reflections on the clinical and laboratory manifestations of altered reactivity provided a conceptual framework within which

allergy emerged as a distinct field of clinical practice and scientific study in the first half of the twentieth century.

The Evolution of Allergy Studies

Just as the original notion of allergy had been strongly shaped by von Pirquet's clinical acumen, so too the subsequent emergence of more focused studies of allergic reactions was embedded in the exigencies of clinical work. During the early decades of the twentieth century, both English and North American pioneers in the study of allergy were primarily concerned with developing novel treatments for clinical conditions such as hay fever, asthma, and food idiosyncrasies, rather than with elucidating more clearly the immunological mechanisms or biochemical pathways involved in allergic reactions. More particularly, early studies of allergy revolved around clinical efforts to refine a specific form of treatment, generally referred to as desensitization or allergen immunotherapy, introduced during the first decade of the century. However, as I shall suggest here, while allergists certainly focused predominantly on perfecting therapeutic approaches to hay fever and asthma in the clinic, they also retained an interest in pursuing experimental studies of allergens and antibodies in the laboratory.

Unlike many aspects of the history of allergy, events surrounding the introduction and refinement of desensitization are relatively well-known.[52] The procedure was developed by John Freeman (1877–1962) and Leonard Noon (1877–1913) working in the Inoculation Department at St Mary's Hospital in London. Funded largely by a lucrative contract for vaccine production with an American pharmaceutical firm, Parke, Davis & Company,[53] the Department was directed by Sir Almroth Wright (1861–1947), whose work focused particularly on developing vaccines designed to stimulate active, rather than passive, immunity against a range of infectious diseases, such as typhoid, cholera, tuberculosis, and staphylococcal skin infections. Initially seconded to contribute to Wright's development of vaccines for infectious diseases, Noon and Freeman began to expand their clinical interest in immunization to the treatment of hay fever.

Convinced that passive immunization with a specific antiserum was both difficult and unlikely 'to bring about a permanent cure', Noon suggested, in a preliminary article published in the *Lancet* in 1911, that 'the induction of an active immunity' to pollen might offer a more satisfactory outcome. He therefore embarked on a series of clinical experiments with the aim of determining 'what degree of immunity can be induced in hay fever patients by inoculations of pollen toxin, how these inoculations may be best regulated, and whether the affection can by this means be permanently cured'.[54] Accordingly he inoculated a small number of hay fever sufferers subcutaneously with increasing doses of an extract of pollen from *Phleum pratense* or Timothy grass, which had been discovered to generate the most active extract. Although he recognized the need for further studies, Noon was cautiously optimistic about the initial results of inoculating his patients:

> The result of these experiments so far is to show that the sensibility of hay fever patients may be decreased, by properly directed dosage, at least a hundredfold, while excessive or too frequent inoculations only serve to increase the sensibility. It still remains to be seen whether the immunity thus attained is sufficient to carry the patients through a season without suffering from their annual attacks of hay fever.[55]

Later the same year, Freeman provided a more detailed account of the procedure. In addition to setting out the protocol that was employed in preparing, quantifying, and administering the various pollen extracts, Freeman carefully charted the dosage and timing of inoculations, clinical estimates of the patients' growing resistance to pollen as measured by the 'ophthalmo-reaction', and the patients' own assessments of the efficacy of treatment. Having dismissed possible sources of error in his results, Freeman was enthusiastic about the impact of desensitization: 'Considering all the cases generally, there seems little doubt that there has been a distinct amelioration of symptoms. This improvement took several forms; a greater freedom from attack, the attack not so bad as in former years, and the attack sooner over, the constitutional disturbance not so great, less asthma'.[56] For Freeman, the absence of a clear explanation for the positive results of pollen inoculation was less important than evidence of clinical efficacy: 'increase in immunity produced by pollen vaccine is in itself the best proof of the soundness of this line of treatment, whether prophylactic or phylactic'.[57]

Significantly, the mode of desensitization adopted by Freeman and Noon did not appear to draw on either the growing physiological literature on anaphylaxis or the speculative pathology which linked experimental anaphylaxis and allergic reactivity with human hypersensitivities; indeed, apart from occasional references to Besredka's work on 'anti-anaphylaxis' and the eventual (but rather reluctant) adoption of the word 'allergy', Freeman's published writings demonstrate a distinct disregard for the blossoming interest in the mechanisms and meanings of allergy and anaphylaxis initiated by Richet and von Pirquet.[58] Nor was Noon and Freeman's innovation overtly inspired by earlier attempts to immunize against hay fever and food intolerance.[59] Instead, the approach to hay fever (and ultimately other allergies) adopted by Noon and Freeman was shaped partly by previous studies of hay fever by Charles Blackley (1820–1900) and William Dunbar (1863–1922), who had identified the pivotal role of what they thought was a 'pollen toxin' in pathogenesis, and partly by trends in bacteriology, in which investigators such as Almroth Wright were attempting to develop active, rather than passive, bacterial vaccines.[60]

Noon and Freeman's method of treating hay fever was rapidly assimilated into clinical practice on both sides of the Atlantic. In Britain, contributors to the *Lancet* reported the outcome of cases treated by Noon's method, debated the most appropriate means of preparing, quantifying and administering pollen, discussed the possibility of vaccinating against asthma, and advertised the availability of commercial 'hay fever reaction outfits' containing pollen extracts prepared at St Mary's and marketed and sold by Parke, Davis & Company.[61] In addition, the technique was adopted and adapted by clinicians in the United States, who devised their own diagnosis and treatment protocols, and who were assisted in the production and distribution of pollen extracts by pharmaceutical companies such as Lederle and Abbott Laboratories.[62] In particular, the technique was developed by Karl Koessler (1880–1925) and Robert A. Cooke. Koessler, a Viennese-trained physician practising in Chicago and later President of the American Association for the Study of Allergy, had worked with Almroth Wright at St Mary's before emigrating to America, where he first began work on active immunization for hay fever in 1910.[63] Cooke, a founding member of the Society for the Study of Asthma and Allied Conditions, cited the contributions of both Koessler and Freeman in his first publication in 1915, and continued to explore the efficacy, safety, and mechanism of active immunization throughout his professional life.[64]

Although American and British clinicians devised slightly different protocols for vaccinating with pollen, commentators on both sides of the Atlantic generally acknowledged that the papers published by Noon and Freeman between 1911 and 1914 constituted the first systematic account of therapeutic and prophylactic inoculation against hay fever and, in the process, ostensibly signalled the birth of clinical allergy in Britain and elsewhere. By providing what appeared to be a viable alternative to climate therapy (see Keirns this volume) and to the wide range of commercial preparations available for asthma and hay fever, the form of inoculation developed at St Mary's became the cornerstone of treatment for allergic disorders worldwide until well after the Second World War. Indeed, the dominance of desensitization survived the introduction of novel pharmaceutical preparations for allergies (such as antihistamines, bronchodilators, and steroids) in the middle decades of the twentieth century and only began to decline in clinical importance after a number of deaths occurred following desensitization during the 1980s.[65] As the prominent German-born American allergist, Max Samter (1908–99), put it in 1979, 'the practice of allergy is virtually synonymous with immunotherapy'.[66]

Closer scrutiny of the evolution of allergy studies during the first half of the twentieth century suggests that developments continued to be shaped largely by the pragmatic concerns of clinical practice rather than by the need to elucidate theoretical issues in the laboratory. Much of Freeman's time and effort at St Mary's, for example, was focused on improving the diagnosis of allergic disorders through the modification of conjunctival and skin tests and on generating better treatment protocols for pollen desensitization. Thus, he experimented not only with the 'leisurely desensitization' that he and Noon had introduced in 1911 but also with 'intensive desensitization' (every day for a week or so) and 'rush inoculation', in which injections were given every hour or two during one day. However, these concentrated courses of inoculation appear to have been designed on an *ad hoc* basis to accommodate the hectic professional and social lifestyles of his patients (particularly perhaps those seen in his private practice) rather than being driven by any clear conceptual rationale for the varying treatment regimes.[67]

Indeed, Freeman was a self-confessed empiricist, regularly emphasizing the centrality of clinical experience (or the 'experiental method') over either theory or statistical evidence.[68] This feature of his work was apparent not only in his flexible approach to establishing therapeutic doses in particular patients, but also in his close descriptions of the cardinal clinical features of patients with allergy (such as the 'allergic nose') and in his liberal use of individual case studies and anecdotes, rather than tables and figures.[69] Revealing the holism characteristic of a certain breed of English physicians in this period,[70] and self-consciously pursuing an appreciation of biological individuality that was increasingly absent from immunological studies, Freeman warned against basing clinical decisions merely on an accumulation of cases:

> It all boils down to this: you must not treat human beings as mere cases – of hay-fever or whatever it may be. You must observe the traditional medical maxim of "treat the individual man" and all his special commitments at the moment; this is as true for us doctors who work in laboratories as for doctors who never go into them. It is especially important when you are deciding whether the patient, though undoubtedly sensitive to grass pollen, is really suitable for a desensitization treatment.[71]

However, although Freeman's curiosity was largely consumed by the challenge of perfecting desensitization through clinical experience, he was not immune to fostering research initiatives both in the clinic and the laboratory. Throughout the 1930s and 1940s, research fellows and visiting scholars affiliated to the Allergy Department not only contributed to Freeman's on-going clinical commitments but also pursued their own research interests, some of which intersected with broader immunological enquiries into the biochemistry of antigen-antibody reactions. During the 1930s, for example, David Harley, a research fellow in the Department funded by the Asthma Research Council, published the results of experiments exploring the nature of antibody-antigen (or more specifically reagin-allergen) mixtures. During the same period, Freeman also encouraged research into the biological polyvalency of pollen allergens, publishing papers himself with W. Howard Hughes, a medical graduate from St Mary's Hospital and an assistant in the Department, as well as supporting the studies of Erich Wittkower (1899–1983) into the 'allergic personality'.[72]

Some years later, when Rosa Augustin (*née* Friedmann) was appointed to the Allergy Department in 1952 with the help of a grant from the Asthma Research Council, she not only carried out, with A.W. Frankland, probably the first controlled trial of desensitization but also published the results of a series of internationally acclaimed studies of both the chemical structure and standardization of allergens and the nature of reaginic antibodies.[73] Augustin's detailed work on immunochemistry was regularly applauded in the Annual Reports of the Wright-Fleming Institute of Microbiology (as the Inoculation Department had been renamed in the 1930s), the self-professed aim of which was to 'foster and engage in research in microbiology and immunology'.[74] The Institute's commitment to immunochemical approaches to allergy, carried out in what was sometimes referred to as an 'immuno-chemistry unit',[75] was bolstered in 1953 by the recruitment of a research assistant, Miss B.J. Hayward, who worked in the Allergy Department with Augustin until they both left in 1960, and subsequently, in more profound ways, by the appointment of the protein chemist Rodney R. Porter (1917–1985) to the new Chair of Immunology in 1959.[76] The contributions of Rosa Augustin to Freeman's allergy empire suggest that, although largely preoccupied with patients in the clinic, allergists were also eager to develop and maintain constructive links between clinical practice and laboratory science.

This collaborative process is evident in Freeman's own writings. Thus, although Freeman was a dedicated bedside clinician, he was also an advocate of close cooperation between the laboratory and the clinic. In his monograph, published in 1950, he pointedly noted that laboratory work had 'always had a practical application to treating the sick who crowded to us', and suggested that 'laboratories and clinics are symbiotic: they are mutually necessary if the work described in this book is to go on'.[77] Freeman's emphasis on the pivotal relationship between laboratory and clinic was partly rhetorical but it was also intimately bound up with his expansive vision of the appropriate organization and delivery of health care services. In 1948, when administrative changes following the National Health Service Act threatened the autonomy of the Department and when the volume of patients seen in the Allergy Clinic was thought to have become 'too cumbersome for research purposes', Freeman stressed to his colleagues on the Department's Council 'the importance of not divorcing the Clinic from the laboratories'.[78] Similarly, in the Allergy Clinic's annual report for 1953, Freeman not only recounted the wide range

of laboratory research and clinical trials being conducted in the Department but also stressed that there was 'close cooperation between the laboratory workers and the clinical material available'.[79] Within his domain at St Mary's, therefore, Freeman was always keen to keep open the 'zone of collaboration' between clinical allergists and laboratory scientists.

John Freeman's preoccupation with immunotherapy and his distinctive blend of clinical practice and scientific research was often reproduced by allergists elsewhere. In North America, as in Britain, allergy practice revolved predominantly around the application and refinement of desensitization, most notably in the clinics of Robert Cooke and Albert Vander Veer (1879–1959) in New York, Karl Koessler in Chicago, and Ransom Claude Lowdermilk (1872–1948) in Kansas.[80] However, like Freeman and his colleagues, American allergists also recognized the importance of pursuing research in the laboratory, and of combining clinical insights into allergic diseases with studies of basic immunological processes. In the 1930s, for example, Robert Cooke published accounts of the possible immunological mechanisms involved in desensitization, introducing the notion of a 'blocking antibody' (later identified as IgG) which was thought to prevent 'the action of allergen on the sensitizing antibody'.[81] In conjunction with Arthur Coca, Cooke also devised a classification of hypersensitivity, including the notion of 'atopy' (or familial predisposition to certain hypersensitivity reactions), which appeared in the *Journal of Immunology* in 1923.[82]

Significantly, Arthur Coca's career exemplifies the nature of the collaboration between allergists and immunologists during the early twentieth century; a practising physician and author of many books on allergic diseases, Coca was also Professor of Immunology at Cornell University Medical College in New York and the founder and first editor of the *Journal of Immunology*.[83] Coca's subsequent appointment as Medical Director of Lederle Laboratories illustrates a further feature of twentieth-century allergy studies, namely the development of close links between allergists, botanists, and pharmaceutical companies in their search to identify and refine more locally specific pollen preparations for diagnosis and treatment. As Gregg Mitman has pointed out, within the realms of North American clinical allergy, research was pursued not only in the clinic and the laboratory but also by ecologists and aerobiologists in the field.[84]

More broadly, the membership and focus of the two major American allergy societies, both founded in the 1920s, also reflected an appreciation of both clinical and laboratory approaches to allergic diseases. Although the Eastern Society boasted a more academic and élite membership of physicians and immunologists, including Robert Cooke, Francis M. Rackemann (1887–1973), George M. MacKenzie (1895–1952), and Harry L. Alexander (1888–1969), it was the Western Society, dominated largely by clinicians keen to popularize their specialty, that had first established an Allergy Research Council in 1929. The express aim of the Council was to promote 'basic research and to urge existing laboratories and research institutes to devote a larger percentage of their funds, resources and energies to a more fundamental type of immunological work'.[85] When the two societies merged to form the American Academy of Allergy in the early 1940s, its members founded a Research Council which not only encouraged both clinical and laboratory research but also facilitated the emergence of a global network of allergists and immunologists by inviting leading international clinicians and scientists, such as Maurice Arthus, Charles Richet, Carl Prausnitz, Willem Storm van Leeuwen (1882–

1933), and John Freeman, to become society members and to speak at conferences.[86] As in Britain, therefore, the promotion of laboratory research remained central to allergists' intellectual agenda and professional identity.

Conclusion

Careful analysis of the origins and evolution of allergy studies on both sides of the Atlantic reveals some historical evidence to support Niels Jerne's assertion that allergy constituted a field of research in which links between the laboratory and the clinic were constructively maintained during the first half of the twentieth century. For Clemens von Pirquet, one of the strengths of the concept of allergy was that it served to unite observations made in the laboratories of experimental physiologists and pathologists with those made by clinicians at the bedside of children in the paediatric wards in Vienna and elsewhere. Thus, allergy neatly captured both the characteristic features of experimental anaphylaxis in animals and the paradigmatic clinical manifestations of vaccination reactions, infections, serum sickness, and a host of seemingly related idiosyncrasies in humans.

As clinical interest in allergy accelerated during the early decades of the twentieth century, the 'zone of collaboration' between laboratory scientists and clinicians persisted. Although John Freeman was primarily a clinician, with little concern for the constraints of regulated research, he nevertheless recognized the manner in which clinical improvements were based on insights offered by laboratory studies of the chemistry of allergens and antibodies. Notwithstanding his evident anxieties about the increasing bureaucratization of the health care services and the fundamental re-orientation in medical thinking that had been wrought by laboratory medicine (also expressed by Lord Horder (1871–1955) and others during the interwar years),[87] Freeman was prepared to integrate the laboratory into his clinical world, using it to reveal and celebrate, rather than silence, both biological individuality and clinical freedom.

John Freeman's cautious acceptance of the laboratory and allergists' willingness to sustain communication and collaboration between the bedside and the bench suggest that although both allergy and immunology were rooted in the late-nineteenth-century expansion of the biomedical sciences, the two disciplines did indeed pursue rather different trajectories during the first half of the twentieth century. Unlike most immunologists, allergists were not wholeheartedly persuaded by developments in immunochemistry nor entirely consumed by the power of the laboratory. While laboratory and field research undoubtedly contributed to the expansion of clinical allergy as a legitimate specialty, both were regarded as subservient to the authority of experience gained in the clinic.

The possibility that the persistent clinical orientation of allergy facilitated the resurgence of immunobiology, in which basic immunological research was once again linked with medical practice, remains speculative. It is certainly the case that some immunologists were interested in allergy, both in Britain and in America, throughout the first half of the twentieth century and that their commitment deepened during the post-war period. It is noticeable, for example, that during the 1940s and 1950s, allergy increasingly attracted the attention of British immunologists who had previously been largely preoccupied with the biochemistry of antibodies and antigens. When the British Society for Immunology was founded in the early 1950s, allergy (along with serological

reactions, biological aspects of immunity, protection against disease, and routine diagnosis) was thought to constitute one of the five major areas of immunological research, and a number of prominent scientists and clinicians working in the field of allergy (such as John Freeman, Carl Prausnitz, Henry Dale, Jack Pepys, and A.W. Frankland) were elected as members or honorary members of the Society.[88] In addition, some leading immunologists, such as John Humphrey (1915–87), who was appointed head of the new Immunology Division at the National Institute for Medical Research in 1957, and who published a major textbook of immunology for medical students in 1963, dedicated much of their professional life to investigating the mechanisms of allergic reactions.[89] Closer integration of allergy and immunology in this period may also have been encouraged by the identification, in 1967, of the antibody involved in many allergic reactions (IgE), thereby reviving beliefs in the biological parallels between hypersensitivity reactions and the mechanisms of host immunity that had been postulated by von Pirquet.[90]

Significantly, the emergence of a 'new immunology' during the 1950s and 1960s was marked not only by a revival of interest in the cellular mechanisms involved in immune responses, but also by growing clinical, scientific and public interest in a range of clinical phenomena, such as transplant rejection, tumour biology, autoimmune diseases, and indeed allergies. This immunobiological turn, in which links between the clinic and the laboratory once again took centre stage, was certainly anticipated, and may have been accelerated, by the 'private line' or 'zone of collaboration' between clinicians and scientists that allergists had established and maintained during the early twentieth century. Although further research on the post-war period is clearly necessary, the predominantly clinical aspirations of allergists, together with their belief in the symbiotic significance of laboratory and clinical work, may indeed have provided a framework or blueprint not only for the emergence of 'clinical immunology', as it came to be known during the 1970s, but also for the immunobiological revolution that infected immunology in the decades immediately after the Second World War.

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Notes

1 Niels Kaj Jerne, 'The common sense of immunology', *Cold Spring Harbor Symposia on Quantitative Biology*, **41**, 1977, pp. 1–4.

2 Idem, 'Summary: waiting for the end', *Cold Spring Harbor Symposia on Quantitative Biology*, **32**, 1967, pp. 591–603. On the development of a 'new immunology' in this period, see: Arthur M. Silverstein, *A History of Immunology*, San Diego: Academic Press, 1989; Anne Marie Moulin, 'The immune system: a key concept for the history of immunology', *History and Philosophy of the Life Sciences*, **11**, 1989, pp. 221–36; Ilana Löwy, 'The strength of loose

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3 Jerne, 'Summary: waiting for the end' (n. 2) p. 592.

4 Anderson, Jackson, and Rosenkrantz, 'Toward an unnatural history of immunology' (n. 2). See also Thomas Söderqvist, 'How to write the recent history of immunology – is the time really ripe for a narrative synthesis?', *Immunology Today*, **14**, 1993, pp. 565–8.

5 Lucia Fisher-Pap, 'Allergy and immunology: wedding of love or marriage of convenience?', *Annals of Allergy*, **34**, 1975, pp. 244–5. See also R. Voorhorst, 'Allergology: past, present and future', *Annals of Allergy*, **40**, 1978, pp. 206–10.

6 Thomas Söderqvist and Arthur M. Silverstein, 'Participation in scientific meetings: a new prosopographical approach to the disciplinary history of science – the case of immunology, 1951–72', *Social Studies of Science*, **24**, 1994, pp. 513–48. See also: Arthur M. Silverstein, 'The historical origins of modern immunology', in Richard B. Gallagher, Jean Gilder, G.J.V. Nossal, and Gaetano Salvatore (eds), *Immunology: The Making of a Modern Science*, London: Academic Press, 1995, pp. 5–20.

7 See in particular: Silverstein, 'The historical origins of modern immunology' (n. 6); Silverstein, *A History of Immunology* (n. 2); Löwy, 'The strength of loose concepts' (n. 2); Anderson, Jackson, and Rosenkrantz, 'Toward an unnatural history of immunology' (n. 2); Kenton Kroker, 'Immunity and its other: the anaphlyactic selves of Charles Richet', *Studies in History and Philosophy of Biological and Biomedical Sciences*, **30**, 1999, pp. 273–96.

8 Michael Worboys, 'Vaccine therapy and laboratory medicine in Edwardian Britain', in John Pickstone (ed.), *Medical Innovations in Historical Perspective*, London: Macmillan, 1992, pp. 84–103.

9 The term was first used by Arrhenius in a series of lectures delivered at Berkeley in 1904 and was later incorporated in the title of his *Immunochemistry: The Application of the Principles of Physical Chemistry to the Study of the Biological Antibodies*, New York: 1907.

10 Moulin, 'The immune system' (n. 2), p. 222.

11 Löwy, 'The strength of loose concepts' (n. 2), pp. 390–1.

12 Ibid., p. 372. See also Ilana Löwy, '"The terrain is all": Metchnikoff's heritage at the Pasteur Institute, from Besredka's "antivirus" to Bardach's "orthobiotic serum"', in Christopher Lawrence and George Weisz (eds), *Greater than the Parts: Holism in Biomedicine, 1920–1950*, New York: Oxford University Press, 1998, pp. 257–82.

13 Löwy, 'The strength of loose concepts' (n. 2), p. 391.

14 Ibid., p. 372.

15 Mark Jackson, *Allergy: The History of a Modern Malady*, London: Reaktion, 2006, pp. 27–55; Ilana Löwy, 'On guinea pigs, dogs, and men: anaphylaxis and the study of biological individuality, 1902-1939', *Studies in History and Philosophy of Biological and Biomedical Sciences*, **34**, 2003, pp. 399–424.

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19 Silverstein, 'The historical origins of modern immunology' (n. 6), p. 11.

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21 Details of von Pirquet's life are in Richard Wagner, *Clemens von Pirquet: His Life and Works*, Baltimore: The Johns Hopkins Press, 1968.

22 Ibid., pp. 28–9.

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CHAPTER FIVE

Germs, Vaccines, and the Rise of Allergy

Carla C. Keirns

> The state of allergy is bounded on the north by the internist, on the east by the dermatologist, on the south by the rhinologist, and on the west by the pediatrician. In fact, this state has been carved out of the territory originally within the confines of the surrounding states and its borders are still ill defined. A great deal of argument, sometimes acrimonious, is going on continually as to the claims of territory by the surrounding states and even the right to separate statehood is opposed by some of the more pugnacious neighbors …[1]
>
> – J. Harvey Black, President, American Association for the Study of Allergy, 1935.

An Austrian physician, Clemens von Pirquet, coined the term 'allergy' in 1906 to describe all of these forms of 'altered reactivity', ranging from what we think of now as allergic diseases (asthma, hay fever, hives) to various idiosyncratic responses individuals had after vaccinations, and, finally, the natural immunity following many infectious diseases.[2] In the first decades of the twentieth century, the nascent allergy community used the terms 'allergy' and 'reaction' to describe any immune response to a substance to which an individual had previously been exposed, encompassing most of what we now think of as clinical immunology.

This paper situates the nascent medical specialty of clinical allergy in Europe and North America, describes its approaches to the diseases of asthma and hay fever, and points to ways in which their theory and practice initially had strong continuities with bacteriology and natural history, in both laboratory techniques and the physiological ideas that inspired them. While immunologic theory and allergy immunotherapy diverged from these origins, practice of allergy in the lab continued to be strongly linked to theories of infection, and in the clinic to medical geographical discussions about climates of health and disease. The practices of allergy immunotherapy developed into a new body of practice and a new set of understandings about the immune system, but the first attempts at analysis of the asthmatic's sputum and development of pollen antitoxins were firmly in the tradition of microbiology, based on understandings of disease which developed from invading organisms and their poisons. The idea that the problem could be the host's immune system arose through the development of allergy vaccines, but was not the vision that initially inspired them.

As part of the growth of interest in the history of immunology, there is now a growing literature on the history of asthma and allergy, and intellectual histories of theories and experiments which advanced modern understandings of the disease have recently been supplemented by broader scientific, social, and environmental histories. Mark

Jackson's work on the history of allergy in Britain explores the foundations of allergy in immunology and the social place of allergy within the British medical profession and the wider community.[3] Gregg Mitman's environmental history of asthma and allergies in the United States is characterized by his focus on place in case studies of hay fever in the White Mountains, asthma in the Rocky Mountains, and ragweed as an ecological scourge of disturbed environments.[4]

Building on this literature, this paper attempts to create an historical bridge between the laboratory traditions of microbiology and immunology and the medical geographic traditions of climatological medicine as they transformed the understanding and treatment of asthma and hay fever (later called allergic rhinitis) in the decades just before and after 1900. Following up on an earlier study of the construction of allergen-free indoor environments, in which allergists fought germs by adopting modernist architectural trends, the current paper emphasizes the impact of germ theory on asthma and the emergence of theories of allergy and the use of the techniques and ideas of bacteriology in the development of allergy vaccines.[5] While there were multiple candidates for microscopic causes of asthma and hay fever, including bacteria, coils, and crystals found in the sputum, pollen soon emerged as the most important of these tiny threats to the nose, throat, and lungs. As a microscopic cause of asthma and hay fever, pollen linked microscopic methods with older traditions of geographic medicine.

Before the beginning of the twentieth century, symptomatic relief for asthma and hay fever consisted principally of change of climate and a variety of symptom-relieving drugs including caffeine, opiates, cocaine, and tobacco. Between 1900 and 1950 a small group of physicians sought to replace climatic therapy, working to sever the persistent link between disease and place. In particular, through an ambitious and highly contested set of strategies they sought to adapt the allergic or asthmatic individual to any climate he or she chose through modification of the patient's local environment and his or her immune responses. In so doing, they established both a medical specialty (clinical allergy) and a distinct mode of medical practice that included a detailed analysis of the patient's home environment and occupation, skin tests for specific allergens, and a new form of desensitization therapy (through vaccinations). Their methods held out the possibility for a multi-dimensional technical fix to a refractory clinical dilemma.

Immunology also offered a scientific explanation for the clinical problem of idiosyncrasy. Until the late nineteenth century, physicians used the principle of individual idiosyncrasy to explain observations that some patients were sensitive to certain substances, including horses, cats, roses, and hay, which had no effect at all on the vast majority of people.[6] Detailed explanations of idiosyncrasy were produced in fields as diverse as heredity, immunology, neurobiology, and psychology, all of which attempted to explain why individuals exposed to the same disease-causing stimuli sometimes developed immunity and other times illness.

The field of allergy has been rooted in two distinct traditions: the first, a medical geographic approach to observing the topographies of diseases and their local and regional causes, and second, a vision of the human body and its responses to bacteria and other substances arising from the traditions and practices of germ theory. These two sets of ideas merged in the pollen theory of the cause of hay fever and asthma, which used geographic arguments about pollen distribution to explain the efficacy of travel in mitigating symptoms, and analogies between bacteria and pollen to explain

the mechanisms of disease. In the first section, we explore the place of asthma and hay fever under the emerging germ theory of disease in the final decades of the nineteenth century. Next, we look at the pollen theory of hay fever and asthma and how it links these new unseen agents of disease with the already established climates of health and illness. Germ theory and pollen studies combine in the creation of pollen vaccines, which are no longer seen as straightforward prophylactics against attacking agents such as bacteria, but instead as modifying the body's immune reactions in myriad ways. This transition from vaccine as booster for natural immunity to modifier of the immune response happened gradually in the laboratories where it was first explored. Finally, while the vaccine treatments for asthma and hay fever attempted to free the sufferer from dependence on favored healthy places, they required the physician to learn the seasonality and geography of pollen distribution in order to use the therapy effectively.

Microscopic Causes of Disease

By the mid-nineteenth century, improvements in glass manufacture and precision instrument manufacture transformed microscopes from expensive custom-made instruments to mass-produced tools available to a wide body of researchers, facilitating first microscopic studies of tissue structure and disease, and ultimately the discovery of microscopic causes of disease. The age-old debates about spontaneous generation and Louis Pasteur's work on fermentation led to extensive use of the new microscopes to study microbes in the air and in the water. From the 1860s to the 1890s, investigators, at first in German and French laboratories, discovered microscopic organisms that they linked to many major animal and human diseases – in short order the bacterial causes of anthrax, cholera, diphtheria, and tuberculosis were identified. After a few spectacular successes, the search expanded, and a race began in which thousands of researchers around the world sought explanations under the microscope to account for many poorly understood diseases. The next stage was for a whole generation of scientific and medical workers to learn to see – and to interpret what they would find – under the 'scope. In these newly-revealed worlds, researchers had to relearn the normal anatomy and physiology that they had formerly known at the level of the naked eye. What were normal findings in blood and phlegm? What were uncommon but healthy variants? And finally, what were clear signs of disease?[7]

As many historians have shown, the germ theory of disease altered both medicine and society, changing the ways that people thought about their bodies and the world around them.[8] The existence of germs changed the way people thought about all diseases. The question, 'Could this be caused by an unknown germ?' had to be asked, even if the answer was ultimately, 'no'. Researchers quickly found that bacteria were everywhere, on the skin, in the mouth and nose, as well as on glasses, plates, and myriad everyday objects. The presence of bacteria in and on the bodies of apparently healthy people presented a challenge to linkages between germs and disease which had to be explained – either these people were immune to these bacteria, or these particular bacteria were not ones that caused disease. The challenge faced by these researchers and their contemporaries was in establishing causality. If a microbe was found in the phlegm of a patient with a disease, did that prove that it was the cause? What about the bacteria found in those apparently perfectly healthy? Koch's postulates, promulgated by the leading German bacteriologist,

became the gold standard for proof that a microbe was the cause of a disease, including isolation of the suspect microbe, growth in pure culture, then reproduction of the disease by exposing a new person to the bacterium.[9] While suited for these narrow purposes, Koch's principles failed to explain the laboratory anomalies of microbes without disease, disease without microbes, and the coexistence of individual microbes with a host of different diseases. These puzzles fed debates about heredity and predisposition, infection and resistance, and the new science of immunology.[10]

Coils, Crystals and Bacilli

Clinical observations that 'animal emanations' from horses, cats, and other creatures caused asthma in some patients led researchers to search for microscopic elements that these animals released, whether germs or otherwise.[11] The most compelling studies, though, came from the examination of the sputum of asthmatics, which showed bacteria, crystals and spiral forms which appeared to be specific to asthma. Circumstantial evidence also came from the discovery of bacteria related to other respiratory diseases. Diphtheria and its associated toxin became a microbial success story when antitoxin started saving children's lives. And while asthma and consumption were frequently seen as distinct diseases before the tubercle bacillus was discovered in 1882, they had been just as often seen as part of a spectrum of disease, as conditions which could transform into one another, or at least as related diseases of the lungs which could benefit from the same treatments. Both diseases were sometimes thought to be caused by the same diathesis, with weak lungs manifesting as asthma in one family member and tuberculosis in another. Most of all, the laboratory orientation that had placed all diseases under the microscope led researchers to search for causes of asthma in the copious, thick sputum produced by its sufferers.

In 1860, when Henry Hyde Salter published his authoritative monograph on asthma, he reviewed the leading theories on the causes of asthma from the eighteenth and nineteenth centuries.[12] He reviewed theories of nervous spasm or paralysis of the bronchi, irritating mucous which caused cough and wheezing, and toxins in the blood, as well as arguments that asthma is not a specific disease at all. Absent from Salter's discussion, but present in monographs on asthma from the 1870s and 1880s, was a detailed microscopic analysis of the asthmatic sputum. In 1853, Jean-Martin Charcot, best known for his work as a pathologist and his descriptions of neurological diseases, published a paper on hexagonal crystals seen in the blood of a person with leukemia and in the sputum of someone with bronchitis.[13] In 1870 Ernst von Leyden expanded on Charcot's observations, arguing that the crystals caused mechanical irritation to the bronchial lining, directly causing the characteristic asthmatic wheezing and spasm.[14] Heinrich Curschmann disagreed with von Leyden, arguing that it was not the crystals but the thick mucous which he noted sometimes came out in the sputum in thin coils which led to difficulty of breathing in asthma.[15]

Other authors pointed to the frequent findings of bacteria in the sputum as well as in the mouth and nose. These bacteria, however, lacked specificity for asthma, being commonly found in other diseases and in the absence of disease. One group of authors explained, 'The number of streptococci in the nasal secretion of hay fever patients greatly exceeds that in the secretion of normal persons. Often streptococci were present in pure

cultures in the case of hay fever sufferers', which implied a claim of causation, in that pure cultures were a requirement of Koch's postulates.[16] The authors went on to say that '*while there are not enough data on hand to permit the assignment of an etiological role to the streptococci found in the nasal cavities of hay fever patients,* these observations certainly tend to compromise the pollen theory of hay fever and should stimulate renewed investigations of this interesting malady'.[17]

British physician J.B. Berkart analysed these debates in an 1889 monograph. He advocated the bacterial origins of asthma based on his observations of the inflammatory quality of the mucous during an attack of asthma, and because he felt that a self-reproducing bacterium could explain how asthma could affect the entire body and progressively worsen for days:

> The clinical peculiarities of Bronchial Asthma plainly indicate the nature of their exciting cause. As has above been shown, the pathological process involved is a progressive form of inflammation … The sero-fibrinous exudation becomes more and more fibrinous, where such is wont to occur; and the consequent mechanical interference with the respiratory function now constitutes the most striking of all its symptoms. No mechanical nor chemical irritant – no foreign body, no abnormally high nor abnormally low temperature, no vaso-motor neurosis, nor anything else, that has hitherto been alleged as a provocative of the disease – can possibly give rise to such a series of phenomena. None of them can exert its injurious influence beyond its immediate point of impact … The agent, endowed with such properties, must necessarily be one, that is capable of reproducing itself. Suspicion, therefore, attaches itself to the various microorganisms, which have previously been described … It shall, at once, be conceded that the mere presence of a micro-organism, however constant it may be, proves absolutely nothing as regards its pathogenic nature. Nor would it serve any useful purpose to refer here to the failures, which attended my numerous attempts to satisfy, as far as possible, the postulates of bacteriological science, in order to arrive at some decision on that point.[18]

Berkart's qualifications about the problem of satisfying Koch's postulates in asthma highlight the difficulty of making either a definitive case for a bacterial cause for disease but also the challenge of dismissing such a theory when it was so strongly held. The bacterial candidates for the causation of asthma eventually faded from favor as the pollen theory of asthma and hay fever was widely adopted. Likewise, the Charcot-Leyden crystals and Curschmann spirals took on the status of curiosities rather than causal agents.

William Osler's 1892 textbook of medicine offered a learned observer's compromise on this debate, explaining the appearance and disappearance of Curschmann spirals and Charcot-Leyden crystals as pathologic markers of the length of an asthmatic attack.[19] First, the sputum appeared as Lännec's perles, which could often be unfolded into collections of Curschmann spirals. Then, in two to three days, as the mucous hardened and decomposed in the bronchial tubes, the Charcot-Leyden crystals would form. These findings, while characteristic of the sputum in an attack of asthma, were seen not as the cause of the disease but its consequence.

Bacterial theories about the origins of asthma persisted, with periodic case reports and discussions in the literature, but the dominant explanations at the end of the nineteenth century were of nervous excitement and pollen intoxication. The evidence for bacterial

explanations was ambiguous, but was best demonstrated by the empiric use of antiseptic inhalers to treat the disease based on the new practice of antisepsis for surgery, which Joseph Lister introduced through his use of carbolic acid in 1869.[20] The treatment was promoted for lung diseases like asthma, bronchitis, and catarrh, as well as influenza and consumption with substances like carbolic acid, phenol, nitric acid, creosote, benzoin, tar extracts, and chlorine inhaled for the purpose of disinfecting the lungs. [21] The use of caustic and acidic inhaled antiseptics to treat asthma continued into the 1920s, long after researchers stopped publishing on possible bacterial causes of asthma, illustrating the distance that often separates medical theory and pharmaceutical practice. But the microbial vision proved important in thinking about pollen, 'animal emanations' and other causes of asthma and hay fever. If these were not infections with living organisms, could they be mediated by some kind of toxin, or did they work in another way?

Pollen, Infusoria and Toxins

Pollen, on the other hand, has had a longer and more successful career as a microscopic cause of asthma and hay fever, as it linked microscopic methods with older traditions of geographic medicine.[22] Pollen explained the seasonality of asthma and hay fever in some patients, the problem of 'rose cold' as well as much of the clinical lore about which places were safe and dangerous for those with asthma and hay fever. The precise mechanism by which pollen produced its symptoms of burning of the eyes, cough, sneezing, congestion, and in some asthma, however, remained uncertain.

The first studies linking pollen to asthma and hay fever were published in the 1870s, in the midst of the discovery of microbial causes of many diseases.[23] Pollen grains appeared to fit smoothly into this new vision of disease from unseen attackers, leading to an explanation of hay fever and asthma as 'pollen poisoning'. Pollen theory explained both the seasonal and geographic features of hay fever and asthma, and allowed for predictions of when and where patients could expect to be free of symptoms. Pollen maps supported the old wisdom that mountains and seacoasts were best for asthmatics, while reducing that clinical observation to a single numerical pollen count. Questions would follow about why some people were susceptible while the majority of the population was not, about the identity of a particular pollen toxin or group of toxins, and innumerable other details. But in the beginning, pollen counters and pollen maps explained much about patterns of illness, and pollen soon formed the foundation of a new set of methods for testing and treatment based on theories of allergy.

Unlike the Rocky Mountains and Desert Southwest, which became the favored new homes for many asthmatics, the White Mountains of New Hampshire became a treasured retreat during the summer and early fall, a gathering place for those asthmatics and hay fever sufferers wealthy enough to take a vacation, and who could also afford the long and arduous trip by ship, rail and carriage.[24] For a significant number of the Bostonians, New Yorkers, and Philadelphians who annually turned to the small towns of the White Mountains as summer retreats from work and city life, these places also afforded relief from their sneezing, wheezing, and misery at home.[25] The United States Hay Fever Association, founded in Bethlehem, New Hampshire, in 1874, dispensed advice about such areas to its members, who consisted primarily of sufferers of hay fever and 'hay asthma' (for those who had both sneezing and shortness of breath) and

interested physicians. A kind of self-help organization, the group met to discuss hay fever and share their experiences with treatments. They combined their findings and produced official tables that, like weather reports, offered the reader an idea of the sort of pulmonary responses they could anticipate in their new locale. Their annual *Manual of the US Hay Fever Association* included as a regular feature a list of places members had visited and been 'exempt' from symptoms. The table from 1892 shows that high mountains and seacoasts dominated the list of favored destinations, though the list of places is most notable for their status as tourist destinations (Figure 5.1).

Locality.	Exempt.	Not Exempt.	Partially, or to particular persons
Adirondack Mtn, interior	3		
Ashland, Wis.	2		
Atlantic City,		1	
Atlanticville,		1	
Ausable,	1		
Barton, Vt.	1		
Bayfield, Wis.,	4		
Beach Haven,		1	1
Bennington Centre,		1	
Berlin Falls,			1
Bethel,			2
Bethlehem,	19	2	
Block Island,		1	1
Blue Mountain, Md.,		1	1
Blue Mountain, Adir.,	2		
Blue Ridge Summit,		1	
California, *	2		2
Campobello,	1		
Cape May,		2	1
Catskills,	1	7	1
Charlevoix, †			1
Chautauqua,		1	
Clayton,			1
Colebrook, N. H.	1		
Colorado, *	1	1	1
Cooperstown, N. Y.,			1
Crawford,	1	1	
Cresson,		1	
Cresson Springs,		1	
Delhi,		2	
Denver,		1	
Duluth,	2	2	1
Eaglemere,		1	
Ellenville, N. Y.,		1	
Europe,	11		2
Fire Island,			4
Franconia,	2		
Gilmanton, N. H.,		1	
Glen House,	1		
Glen Summit, Pa.,		1	
Grand Isle, Mex. Gulf,			1
Halifax,	1	1	
Jefferson,	6		
Kaaterskill,	1		
Keene Valley,	1		
Lake Bomesen,		1	
Lake George,	1		
Lake Mohonk,		1	
Lake Placid,	1		
Lake Superior Region,	1		
Lansdowne, Can.,	1		
Leeds, Can.	1		
Litchfield,			1
Littleton,			1
London, Eng.,	1	1	
Los Angeles,		1	
Mackinac, †	1	3	1
Maine Coast, ‡	‡2	1	
Marquette,	2	1	
Minneapolis,		1	
Montpelier,		1	
Montreal,	1	1	
Mountain Lake Park,		1	
Muskoka,	2		
Nantucket,	1	1	
New Jersey Coast,		4	
North Conway,		2	
Oakland, Md.,		2	1
Ocean—to most people,			
Ottawa,		1	
Overlook Mtn House,		1	
Pasadena,		1	
Petoskey, †	1	1	1
Pittsfield, Mass ,		1	
Pocono,			1
Pompeii, N. Y.,	1		
Port Arthur,	1		
Prince Edward Island,	2		
Put in Bay,			1
Quebec,	3	1	
Quogue,		1	
Rangeley Lakes,	4		
Richfield Springs,		1	
San Diego,	1	1	
San Francisco,	2		
Saranac Lake,	1		
Santa Barbara,		1	
Saratoga,		2	
Schroon Lake,		3	
Shellburne,			1
Saulte St. Marie,	2		
St. Andrews, N. B.,	4		
St. Paul,		1	
Sugar Hill,	4		
Thousand Islands,		2	
Twin Mountain,	3		
Upper Bartlett,		1	
Watch Hill,		2	
Waterville, Me.,		1	
Wernersville,		1	
White Mountains, ⁂			

* High regions of
† Suffered mildly.
‡ One sailed off it; the other drove along it.
⁂ Generally exempt, with few or partial exceptions.

Figure 5.1 Exempt places from hay fever (1892). Source: Survey of the Membership, *Manual of the United States Hay Fever Association*, 1892.

Many of the visitors to the White Mountains during the autumn hay fever season (late August and early September) had medical or scientific training, and these visitors sought explanations for why they felt well in New Hampshire and ill at home. In keeping with the scientific discoveries of the day, the discussion was dominated by talk of miasmas, spores, animuncules, infusoria, mites and other microscopic culprits which might be carried on the air unseen, and which might die with the autumn frosts – just when symptoms were almost universally relieved each year. As Secretary of the association, Edmund S. Hoyt discussed the causes of hay fever as he understood them, emphasizing both local atmospheric factors and individual idiosyncrasy:

> It is evident that whatever may be the occasion of Hay-Fever in the physical idiosyncracies [*sic*] of the victim, the real causes of it exists in circumstances external to himself, and over which he has, or may have, more or less of control, and that those circumstances are atmospheric, or, in other words, that the atmosphere is the bearer of the specific poison, whatever it be, whether it be *miasmatic, sporadic or animalcular* … it is evident that these atmospheric influences are periodic … it is evident that these atmospheric influences are local in their character, and this is the great comfort which your secretary has to bring you in all your affliction. Time one may not annihilate, even by sleep, but localities may be selected, according to the liking, or, according to the purse. Medicine may accomplish little or nothing, and it is safe to say, notwithstanding the protestations of interested parties, that medicine has yet accomplished little or nothing, yet there is 'balm in Gilead,' and in Gorham, and in Bethlehem, too, and in numberless regions known and perhaps unknown.[26]

Many physicians and scientists in the association published on both their personal experience of hay fever and experiments and observations about the disease. By the end of the 1870s, for example, Dr. Morrill Wyman of Harvard Medical School – whose family had been traveling to the White Mountains for some years – was, like his British counterpart Dr. Charles Blackley of Manchester, England, arguing that pollen was the major exciting cause for asthma and hay fever. Its appearance coincided with intensification of symptoms in the summer and fall, and such a concept fit the most modern theories of the day – finding the causes of disease in microscopic particles. Neurologist George M. Beard called the pollen hypotheses the 'infusorial' theory of hay fever, linking it explicitly with germ-based explanations of disease.[27] Morrill Wyman's experiments in this vein began with the observation that he and his family suffered in Boston in the late summer and fall, and found relief in the White Mountains. Wyman conducted a series of studies of pollen and its relationship to hay fever and asthma, paying special attention to the geographic distribution of pollens. When Wyman published his book on hay fever in 1872, he included several maps of pollen distribution during peak season in the United States, which he had developed from his wide correspondence with physicians and hay fever sufferers. The frontispiece featured his favored White Mountains region (Figure 5.2).[28]

In parallel with Wyman's observations, British physician Charles Harrison Blackley studied the relationship between pollen counts and symptoms of hay fever and hay asthma with a novel device. He invented a 'pollen counter' which featured a microscopic slide covered with a layer of sticky glycerine and left outside to catch pollen in a birdhouse-like apparatus with a roof but no walls. Rather than geographic variation, Blackley's

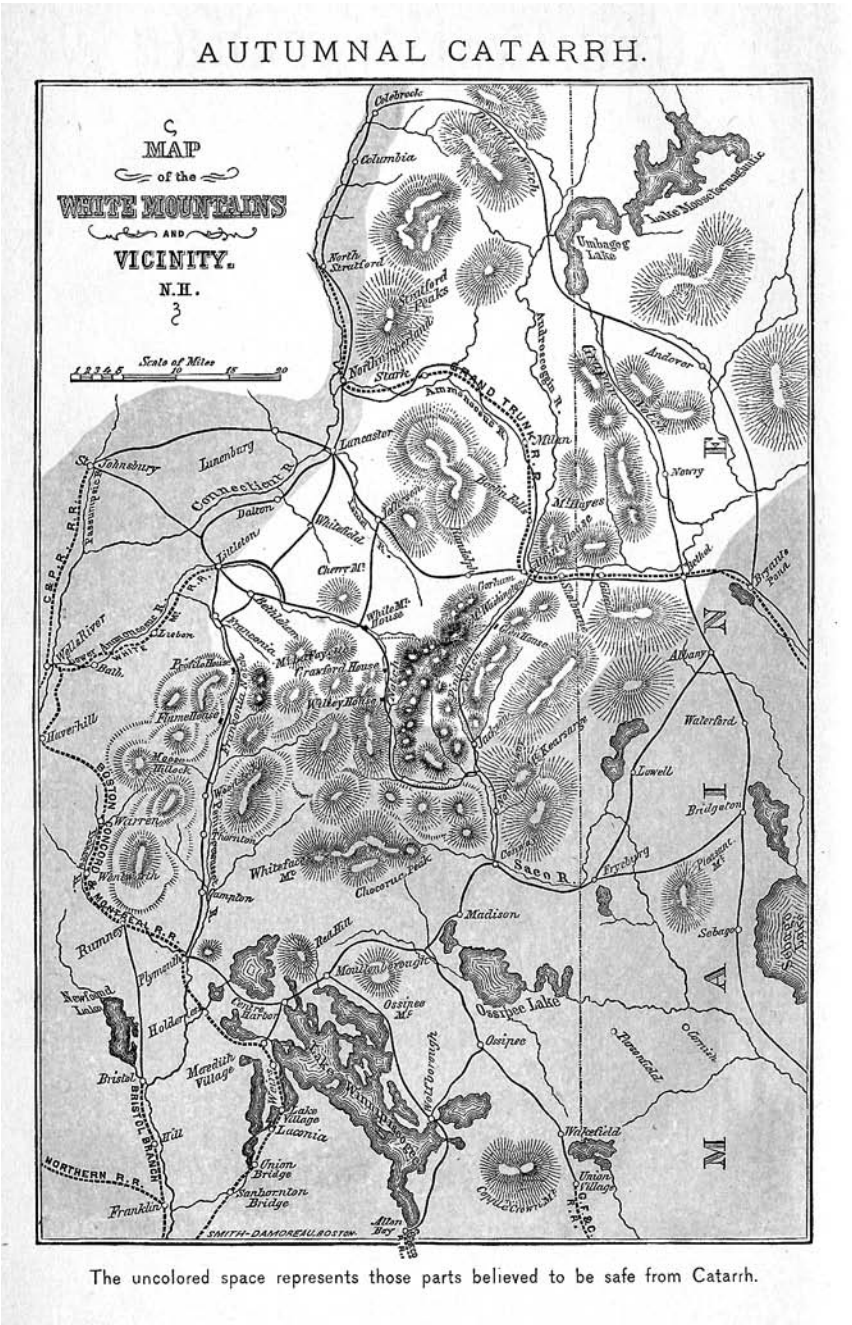

Figure 5.2 Map of the White Mountains and Vicinity. The light area in the middle of the map was considered exempt from pollen. Source: Morrill Wyman, *Autumnal Catarrh (Hay Fever)*, New York: Hurd & Houghton, 1876, frontispiece.

work illustrated seasonal variation, with day-by-day counts from May to August which showed late June peaks 20–50 times his counts from early May or early August.[29] This illustration from his book, *Experimental Researches on the Causes and Nature of Catarrhus Aestivus,* published 1873, shows the pollen counter, and the graph following shows daily pollen counts for the summer of 1866 (Figures 5.3 and 5.4).

Despite the first rush of enthusiasm for pollen counts, Wyman, Blackley and others soon found that individual cases responded differently to the same counts. Individuals

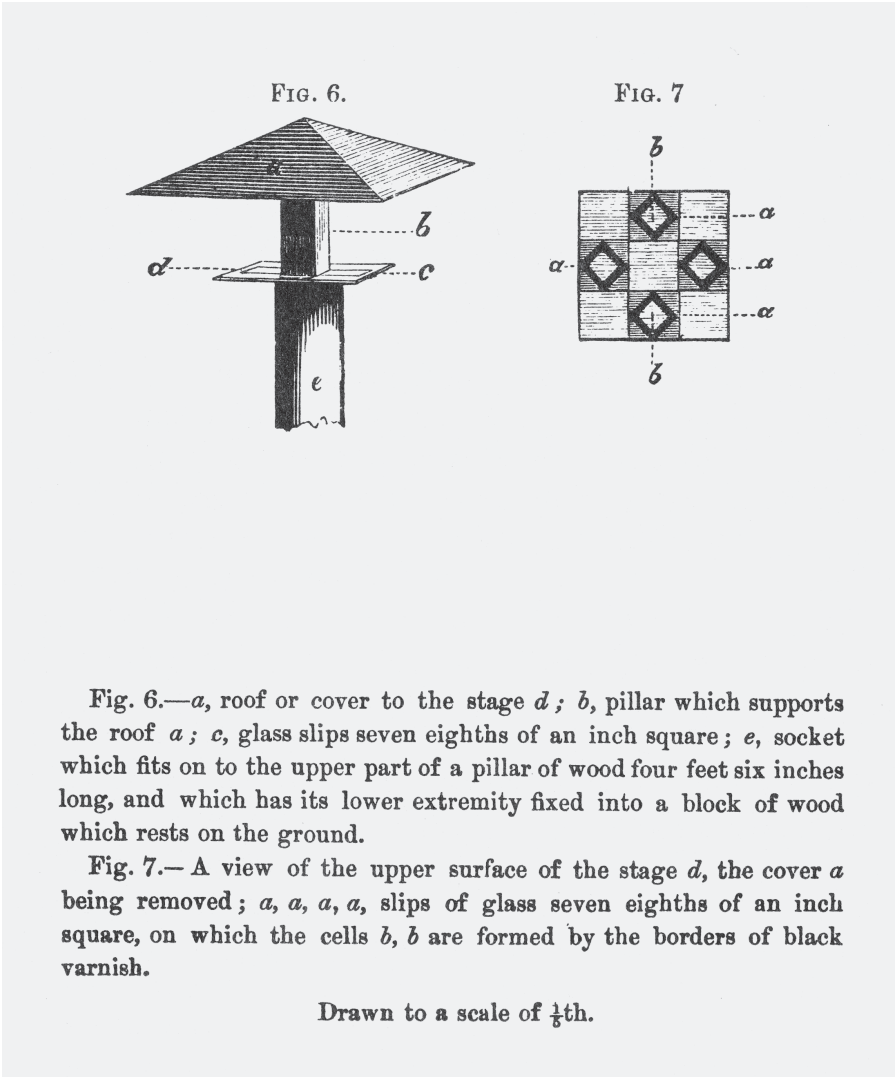

Fig. 6.—*a*, roof or cover to the stage *d*; *b*, pillar which supports the roof *a*; *c*, glass slips seven eighths of an inch square; *e*, socket which fits on to the upper part of a pillar of wood four feet six inches long, and which has its lower extremity fixed into a block of wood which rests on the ground.

Fig. 7.— A view of the upper surface of the stage *d*, the cover *a* being removed; *a*, *a*, *a*, *a*, slips of glass seven eighths of an inch square, on which the cells *b*, *b* are formed by the borders of black varnish.

Drawn to a scale of $\frac{1}{8}$th.

Figure 5.3 Pollen counter used by Charles Blackley, with glass slide covered with glue and placed under a roof to collect only airborne particles. Source: Charles H. Blackley, *Experimental Researches on the Causes and Nature of Catarrhus Aestivus*, London: Ballière, Tindall & Cox, 1873, opposite p. 122.

differed in their reactions and showed variations in symptoms when they stayed in the same place. Competing explanations for the disease persisted. Samuel Lockwood, a member of the Association, explained the state of hay fever and hay asthma pathology in 1890:

> I think that writers generally on this disease are too apt to specialize in theory. The very nature of the malady is a temptation in this direction, since it exhibits such a complication of symptoms, and is accredited to so many and diverse causes. One ascribes it mainly to summer heat; another to dust in general; another to pollen in especial; and still another to a peculiar microbe, which he calls diplococcus … I hesitate not to express my belief that Hay-Fever in its advanced stages is the collective effect of all the causes stated.[30]

While crediting pollen with causing much of the suffering of hay fever and 'hay asthma', Lockwood went on to argue that: 'This pollen theory, as a sole, or main cause of Hay-Fever, has been unduly magnified, and should be given up. I am now convinced, however, that of all the atmospheric dust it is the most irritating'.[31]

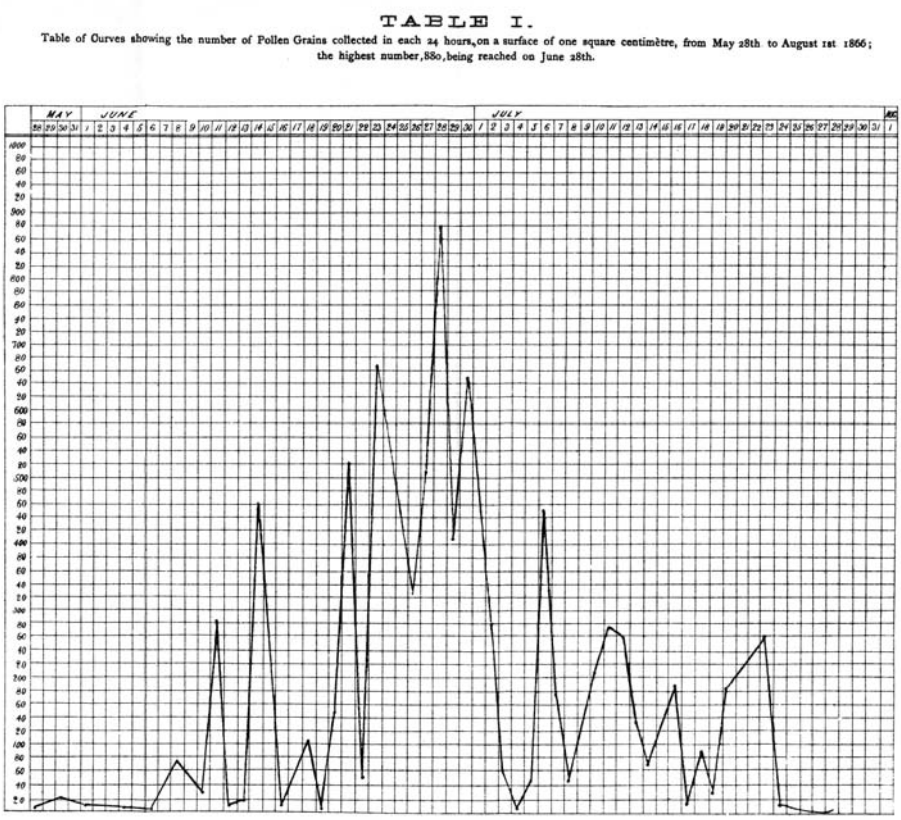

Figure 5.4 Graph of daily pollen counts. Source: Charles H. Blackley, *Experimental Researches on the Causes and Nature of Catarrhus Aestivus*, London: Ballière, Tindall & Cox, 1873, opposite p. 129.

Beard, also a member of the association, offered an alternative explanation by building on the widespread belief that asthma and hay fever were nervous diseases restricted to the upper classes.[32] He wrote about hay fever as part of a family of enervating diseases of civilization afflicting the new urban American élite. While Beard's work was respected, and hay fever earned a place among the nineteenth-century nervous diseases, this designation did not exclude a role for pollen in causing the disease; it rather specified why certain individuals seemed especially sensitive to it.

By the 1910s, the pollen theory had been widely accepted. The correlation of the temporal and geographic appearance of pollen with wheezing and sneezing made a compelling case, but it was one that had not yet been explained through a pathological mechanism. Such a theory would have to account for not only the connection between pollen and the symptoms of asthma and hay fever, but also the puzzling individual idiosyncrasies in the diseases. Starting in the 1890s, William Philips Dunbar in Germany would begin to explain the links between pollen and asthma and hay fever as a reaction mediated by a specific, soluble pollen toxin, and to develop vaccines for that toxin.

The Rise of Allergen Immunotherapy

The science of immunology that underlies twentieth-century explanations of allergic diseases such as asthma arose from nineteenth-century successes in fighting infectious diseases. The desire to improve existing immunizations and antisera, and to develop new therapeutic agents, led researchers to explore more carefully the mechanisms of immunity from infection, both naturally occurring and vaccine-induced.[33] In the first decade of the twentieth century, disturbing reports that some individuals were becoming ill after receiving potentially life-saving antisera added to the urgent need to understand more about the human immune system. As an accumulating number of clinical accounts demonstrated, foreign serum could produce a slow reaction called 'serum sickness', or an acute and fatal form which Charles R. Richet (1850–1935) dubbed 'anaphylaxis', or a kind of 'anti-protection', to contrast it with the normal 'prophylaxis' from the serum.[34]

This model of anaphylaxis was widely used (and many argued misused) in the first two decades of the twentieth century, applied to everything from gastroenteritis to eugenics, but it had special resonance for those who studied asthma.[35] The commonalities between anaphylaxis and asthma included triggering of an attack by exposure to foreign protein and the resulting shortness of breath and feeling of suffocation, which led to widespread application of the concepts of anaphylaxis to the study of allergy. Dr. S.J. Meltzer, of the Rockefeller Institute for Medical Research, explained: 'The theory is here offered that asthma is an anaphylactic phenomenon; that is, that asthmatics are individuals who are "sensitized" to a specific substance and the attack of asthma sets in whenever they are "intoxicated" by that substance'.[36] Meltzer went on to describe in detail the relationship between nerves and muscle fibers deep in the lung. But his principal point was that asthma was a toxic response like anaphylaxis rather than a nervous reflex, the mechanism behind contemporary theories of nervous asthma. This comparison with anaphylaxis placed asthma squarely within the realm of a new immunology.

Though vaccinations, allergies, and serum sickness seemed initially to constitute divergent processes, early immunologists recognized that in each case a previous exposure to a substance could change an individual's response to that substance when

they encountered it again. Individual variation in responses to the environment could be accounted for in immunological terms, based in a combination of hereditary predisposition and life experience. Contemporary theories of protein sensitization set two prerequisites to an asthmatic reaction to a specific substance such as a pollen: first, it had to be in a susceptible individual (a condition that seemed to travel in families), and secondly, the allergic response followed an earlier exposure.[37] When von Pirquet coined the term 'allergy' in 1906 he used it to describe all of these forms of 'altered reactivity', ranging from what we think of now as allergic diseases (asthma, hay fever, hives) to responses to vaccinations, and, finally, the natural immunity following many infectious diseases.[38] This usage of the term 'allergy' to describe all immune responses, protective or deleterious, was not widely accepted, with most practitioners instead using it synonymously with hypersensitivity reactions, though the use of the term was certainly in flux for some time (and arguably still is).[39]

Visions of the immune system as a cause of disease were only beginning to emerge when the first serious attempts were made to modify response to pollen in hay fever and asthma.[40] So while the terms and concepts of allergy and anaphylaxis would come to define allergy immunotherapy, initial attempts at vaccination were based, instead, on theories of hay fever and asthma as infectious diseases, either resulting from direct infection or a toxin akin to diphtheria.[41] Both the vaccines against hay fever created by H. Holbrook Curtis, a New York physician, and the 'Pollantin' antitoxin developed by Dunbar, for example, were derived from the previous generation's work linking pollen to asthma and hay fever.[42]

Pollen Toxins, Antitoxins, and Vaccines

By the 1910s, these trends had become organized around three research groups centered around Dunbar in Germany, Almroth Wright in Britain, and Robert Anderson Cooke in the United States. These emerging allergists offered courses of 'desensitizing' immunizations along with other approaches, to try to accommodate their patients to climates and occupations that they could not avoid through relocation or retraining.

Dunbar (1863–1922) was an American physician from St Paul, Minnesota, who, in the last decades of the nineteenth century, followed the path of many ambitious young scientists. He traveled to Germany to learn the new microtechniques, eventually earning his medical qualification at Giessen in 1892 before becoming swept up in a devastating cholera epidemic in Hamburg during which he was credited with improving the detection of cholera in the water supply and thereby helping to eradicate the disease.[43] He spent the rest of his career in Germany, eventually rising to the position of Director of the State Hygienic Institute in Hamburg. Best known for his work on sanitation, he had a side interest in hay fever, which sharpened every spring when his own symptoms worsened.[44] Dunbar laid out his vaccine treatment of hay fever and asthma as the only alternative to physical methods of avoidance such as masks or relocation:

> Since the discovery of the etiology of hay-fever it has been evident that there are only three ways by which the disease can be successfully treated. The first is to search for localities free from the specific agent; the second to employ apparatus to protect the eyes,

> nose and mouth of patients from contact with such agents; the third to immunize the patient actively against pollen toxin or to use a specific antidote.[45]

The ways in which Dunbar's expectations were shaped by his work on bacteria, and on the receptor-specificity theories of Paul Ehrlich, are apparent in his own description of his work: 'I advanced the theory that hay-fever is a disease caused by vegetable poisons contained in the pollen of certain plants. These substances were connected with the proteid of the pollen grain and of a highly specific character'.[46] He went on to say that 'for hay-fever patients the proteid of active pollen is a toxin comparable to abrin, ricin, diphtheria toxin, etc'.[47] While the clinical manifestations of hay fever were not as dire as those of the other deadly and recently-discovered toxins he listed, Dunbar argued that his procedures for chemical isolation of the active extract of pollen were consistent with fractionating a toxin from a bacterium, a toxin which would, in time, be further characterized.

Dunbar's arguments about the specificity of his solutions were somewhat inconsistent. He argued that there were distinct reactions to grasses, North American ragweed, and cat saliva, and that a person sensitive to one may be impervious to the others, but also argued that most would respond to a generic 'Pollantin' as the common factor in each might be an identical toxin. He described a case of a woman whose sensitivity to her cat responded to treatment by the pollen antitoxin. He explained this curious situation by arguing that the sensitivities to cat and pollen were of a kind: 'The case appears particularly important to me because such idiosyncrasies to my mind are very nearly related to hay-fever, for otherwise it would be impossible to influence them favorably by pollen antitoxin'.[48]

As with many researchers, he performed a large series of experiments on himself and his assistants, with the hay fever sufferers in his lab serving as subjects and those without the condition as controls. Following the techniques of bacteriology, Dunbar's group worked to obtain pure supplies of pollen, and prepared multiple extracts to determine the active element, testing these solutions on the conjunctiva (in the eyes) of the hay fever sufferers who worked in his lab. Once the active extracts were isolated, they were injected into horses and rabbits to produce Pollantin, the manufacture of which they contracted out to Schimmel & Company in Miltitz, a local chemical, drug, and perfume manufacturer. Patients could choose from an antitoxin for injection, a powder form which could be applied to the mucous membranes, an ointment, and pastilles. Though most preparations were made from horse serum, Pollantin R, the rabbit serum, was available for those who had reactions to horse serum.

A competing remedy, Graminol, was introduced by Wolfgang Weichardt of Erlangen, who had served as one of Dunbar's assistants. Graminol was derived from the serum of ruminants, presumed to be naturally exposed to pollinating grasses by their grazing, rather than through a process of injecting purified pollens and later isolating a specific antiserum. The precise constituents of the formula were, however, secret, and Dunbar in discounting this 'nonspecific' serum (as opposed to his laboratory prepared antisera) argued first that there was little chance that exposure via the digestive tract would produce natural immunity because of breakdown of proteins, and, second, that the true active ingredient in Graminol was adrenaline.[49]

As Dunbar's group continued their work on pollen and Pollantin, they were disturbed by increasing reports of reactions to horse serum preparations, both in their patients and in those receiving antitoxins for diphtheria and tetanus. The substitution of rabbit serum did not solve the problem, however. In fact, an even larger percentage of their hay fever patients appeared to develop sensitivity to the rabbit serum form of Pollantin than to the horse once they started using it. Dunbar presented his dilemma as follows:

> The occurrence of horse serum anaphylaxis in hay-fever patients using pollantin has led me to pursue my investigations on this subject since 1905. All endeavours to prevent it have been in vain. On the other hand I found that it only occurred in a comparatively small percentage of cases, and that it then is regularly an indication of a decline in the hay-fever predisposition … Nevertheless this condition was not desirable, especially since the alternative use of antitoxin from the rabbit was also soon followed by anaphylaxis. Such experiences convinced me of the desirability of recommencing experiments on *active immunization*.[50]

Dunbar's group was not the only one pursuing immunization strategies for hay fever and asthma, with the early efforts of Curtis supplanted by systematic efforts in Britain and the United States by some of the leading immunologists of the early twentieth century.[51] The precise meaning of 'antisera' and 'vaccine' was still in flux, and the scientists themselves were still trying to understand the mechanisms for their largely empiric treatments. Antiserum was generally used after exposure to a bacterium, and had as its goal treatment, such as with diphtheria antitoxin used to fight outbreaks. Vaccines were initially preventive, as with the use of the Vaccinia virus to prevent smallpox. But in the early twentieth century, as the science of immunology was developing rapidly, the boundaries of vaccine therapy were open, with preventive strategies well-established, but with many researchers working to show the value of deliberate manipulation of the immune system with vaccines at every stage of illness. It was no accident that allergy desensitization should emerge in the Department of Inoculation run by Sir Almroth Wright.

Sir Almroth Wright (1861–1947) was the leading proponent of vaccine therapy in Britain in the early twentieth century.[52] Wright established the Inoculation Department at St Mary's Hospital in London soon after his appointment in 1902 to the pathology staff. His department was concerned with the therapeutic possibilities of vaccination against infectious diseases, and Wright was a leader in promoting the potential of vaccines to prevent and treat infections.[53] Wright developed a relationship with the Parke Davis Company, who had the right to produce and market vaccines developed at St Mary's and split the profits with the Department to support its research and clinical activities. By 1907, Wright had been joined by John Freeman and Leonard Noon, young physicians who had studied together at the Pasteur Institute in Paris. While most of the work of Wright's laboratory was directed to fighting pneumonia, boils, and other bacterial diseases, Noon and Freeman developed a program in hay fever vaccines which both would continue for the rest of their careers.

After working on several other projects, Noon and Freeman began experimenting in 1908 with vaccines for hay fever. In his first publication on the topic, Noon immediately adopted Dunbar's pollen toxin theory: 'Hay fever is a form of recurrent catarrh affecting certain individuals during the months of May, June, and July. It is caused by a soluble

toxin found in the pollen of grasses. The patients present the idiosyncrasy of being sensitive to this toxin, which is innocuous to normal individuals'.[54] But in opposition to Dunbar's extensive work on antisera, both Noon and Freeman were committed to direct immunization with pollens – so-called 'active immunization' – both because it avoided the problems Dunbar had encountered with serum reactions, and because they reasoned that if the patient's own immune system produced a protective response, it might be lifelong (in contrast to the temporary protection offered by antisera). As Noon explained, 'The local application of a specific serum, such as pollantin, offers a reasonable method of treatment, but one which is difficult and laborious, and which is not calculated to bring about a permanent cure'.[55]

Their initial clinical trials demonstrated both qualitative and quantitative success: 'The result of these experiments so far is to show that the sensibility of hay fever patients may be decreased, by properly directed dosage, at least a hundredfold'.[56] But they continued to depend upon careful calibration of the pollen dosage to the individual patient's state of reactivity. After Noon's premature death from tuberculosis in 1913, Freeman carried on their work on hay fever inoculation, reporting in 1914 on their first three years of clinical experience:

> The 84 cases have between them experienced 113 hay fever seasons after – or under – treatment. The results of these summers are as follows:
>
> In 34 seasons (30.1 per cent.) the hay fever was completely cured or was so slight as to be insignificant.
>
> In 39 seasons (34.5 per cent.) the hay fever was greatly diminished.
>
> In 27 seasons (23.9 per cent.) the hay fever was admittedly diminished, but only to a slight extent.
>
> In 13 seasons (11.5 per cent.) the hay fever was no better, and of these, two cases reported that they were worse.[57]

Freeman continued his work on hay fever until his death in 1962. In keeping with the atmosphere of Wright's Inoculation Department, and perhaps inspired by the financial imperatives to produce the profitable 'Pollacine' series of vaccines, Freeman concentrated on the practical issues of extracting pollen, formulating vaccines, and techniques and schedules of administration. He left scientific matters such as the mechanism of allergy immunotherapy to others.[58] By 1915 several other researchers had published their work on hay fever vaccines, but that of Robert Anderson Cooke (1880–1960), Arthur F. Coca (1875–1959) and their colleagues in New York stood out for their careful laboratory methods, commitment to standard procedures, and extensive research into the mechanisms of human sensitization and the precise immunological responses patients had to treatment.[59] Cooke and Coca became known for their rigorous laboratory-based investigations, which yielded improved practical tests such as skin tests for sensitization to replace the ocular tests used by Dunbar and Freeman and a means of standardizing strengths of pollen extracts.[60] Skin tests for allergenic sensitivities, for example, had the advantage of allowing testing for many different allergens at once.

In the 1920s and 1930s, Cooke and his team, using techniques such as transfusion and serum injections from inoculated hay fever patients to those who had not undergone desensitization treatments, postulated the existence of a 'blocking antibody'

which interfered with the interaction between the pollen grain or other allergen and the sensitized cells of the patient:

> Using ragweed hay fever as the representative of a certain type of allergy we have made studies to determine if possible the mechanism of the protection afforded by specific injections thus far established only by clinical observation.
> 1. Blood transfusions and serum injections from clinically immune, treated patients stopped the clinical reaction in untreated patients, thus indicating a transferable immunity.
> 2. The amount of skin sensitizing antibody in the serum was found to be practically unchanged by specific injections.
> 3. Injection of allergen-antibody mixtures into normal skin showed an immediate (1 hour) reaction when sites were made if serum of untreated cases (Serum A) was used but none or slight reaction if serum of treated cases (Serum P) was used.
> 4. When sites made with allergen-antibody mixtures were tested after 48 hours, reactions were absent with Serum A mixtures if enough allergen had been used, but were positive with mixtures of Serum P even though a much stronger allergen was contained in the mixture.
> 5 The primary inhibition of reactions with mixtures including Serum P was not due to antihistamine effect nor to binding of skin sensitizing antibody nor to binding or lysis of allergen.
> 6. The inhibiting antibody appears to be specific.
> 7. These serological studies supported by transfusion experiments have been interpreted by us as showing the development under treatment of a peculiar blocking or inhibiting type of immune antibody that prevented the action of allergen on the sensitizing antibody and hence showed in the type of human allergy under consideration (hay fever) the coexistence of sensitization and immunity.[61]

While early confirmations such as that by Francis Rackemann's team at Harvard helped the 'blocking antibody' theory gain currency, continuing studies of the mechanisms of allergen immunotherapy would reveal additional immunologic mechanisms.[62] From a purely clinical perspective, responses to allergy shots varied substantially from one patient to the next, just as the symptoms of allergic diseases themselves had. As an early twentieth-century researcher complained: 'nothing is more difficult to explain than why any particular method of treatment should cure one case and have no effect on another which is apparently exactly similar. The recognized practices of bacteriology show strange misfits when applied to asthma'.[63] This individual variation confounded both standardization of procedures – which were often customized to the patient – and evaluation of the therapeutic value of allergen immunotherapy. In the 1940s and 1950s, A.W. Frankland and Rosa Augustin, both members of Wright's institute and both well aware of the new standards for blinded, placebo-controlled clinical trials, set out to study the benefits of allergen immunotherapy.[64] During the summer of 1953, they received support from the Asthma Research Council to study 200 patients who were sensitive only to grass pollen and had never received injections for hay-fever. Half received one of two active vaccines and the other half received one of two inactive controls. Seventy-nine per cent of the hay-fever patients reported good or excellent results following pollen vaccines, while thirty-three per cent of those receiving control vaccines reported good or excellent results, both evaluated by daily symptom diaries as well as the patient's overall

impression of the success of treatment at the end of the summer.[65] Likewise, Francis C. Lowell and William Franklin at the Massachusetts General Hospital studied ragweed pollen injections over the summers of 1959 to 1963. They also found improvements in those receiving ragweed extracts over controls, but their papers are more notable than the British group's for their frustration with daily and weekly variations within as well as between groups – ultimately they found a modest, but real effect in favor of pollen injections.[66]

Allergy in Practice

After these initial developments, the practice of allergy immunotherapy still required substantial standardization of techniques and reagents. Even after Parke Davis in Britain and Lederle Laboratories in the United States began commercial production of pollen vaccines, there were problems in supply, variations in concentration, and limits to the number of different extracts available, which was a particular problem because of different regional ecologies of hay fever plants. Sometimes, practitioners had to collect and purify their own antigen preparations for diagnostic and therapeutic use. In some cases, a particular item was not commercially available; in others, the dosage had to be modified according to the sensitivity of the individual patient, since even early attempts to create standard solutions by weight, protein content, or nitrogen content did not correlate with allergenic strength. This proved an ongoing problem, and many methods

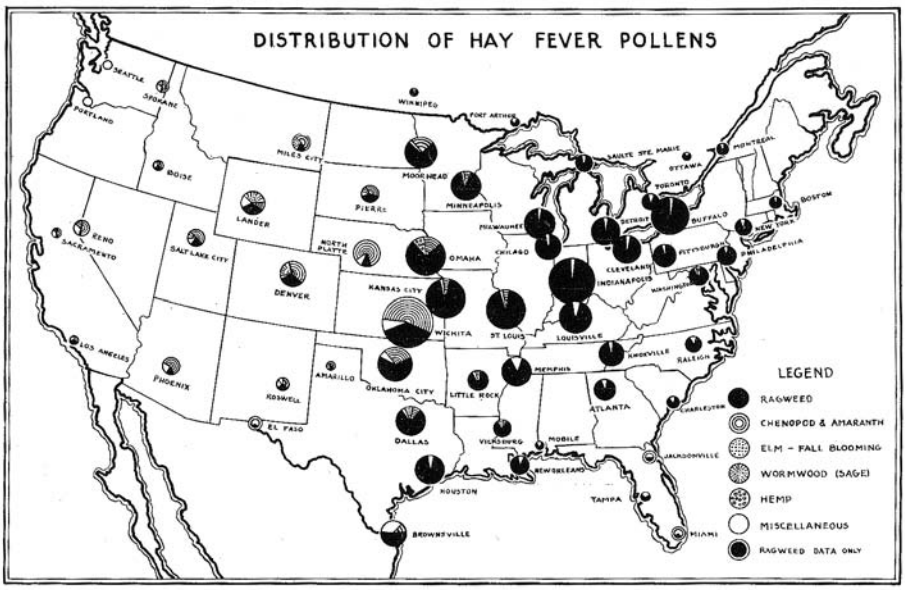

Figure 5.5 Map produced by O.C. Durham (Abbott Laboratories) demonstrates both overall pollen counts and the species of plants representing most airborne pollen. Source: O.C. Durham, 'The Pollen Content of the Air in North America', *Journal of Allergy*, **6**, 1935, pp. 128–49 at p. 129. With permission from the American Association of Allergy, Asthma & Immunology.

were developed to create and measure the clinically-relevant strength of pollen and other allergen desensitizing vaccines. Over the years, working groups and professional societies of allergy have taken this project to facilitate both intellectual dialogue and therapeutic safety and effectiveness.[67]

An irony of allergy practice in the early twentieth century was that the allergists' determination to free patients from the constraints of geography required that these physicians themselves obtained a detailed local knowledge of the plants in the region where they practiced. This was essential both so that they would know what their patients might be sensitive to, and to enable them to prepare allergen extracts. Even after commercial companies began producing vaccines for allergy, the allergist still had to know his local ecology, the distribution of allergy-inducing plants in his local region, and be able to produce his own extracts when commercial vaccines were not available for local hay fever plants.[68] In order to improve understanding of the epidemiology of allergic diseases and to guide clinical practice, pollen surveys were conducted across the country, some by clinics, others by public health authorities, and others by botanists employed by the companies selling pollen extracts (Figure 5.5).[69] Botanist Oren C. Durham, for example, started collecting pollens in 1916 for his brother-in-law R. Claude Lowdermilk, who published one of the earliest studies of pollen vaccines. Durham then started working for William Duke, an early president of the American Association for the Study of Allergy, and finally did extensive work with Abbott Laboratories in the production of many pollen vaccines.[70] Botanist Roger Wodehouse started his work on pollen grains when he was a graduate student in plant physiology at Harvard and began to collect material for Dr Joseph Goodale's allergy patients at Massachusetts General Hospital. Wodehouse helped produce vaccines at the Arlington Chemical Company while working on his doctorate at Columbia, and then directed work on pollen vaccines at Lederle Laboratories with Coca.[71]As Mitman has shown, partnerships between allergists, botanists, and pharmaceutical companies were critical to the establishment of vaccine treatment of allergy, but the pharmaceutical companies' plans to create a single, universal pollen vaccine for all patients and all regions of the country ultimately proved futile.[72]

In 1923 and 1924, two allergy societies were founded in the United States: a western group founded in San Francisco as the Western Society for the Study of Hay Fever, Asthma and Allergic Diseases (later renamed the Association for the Study of Allergy) and an eastern group based in New York founded the Society for the Study of Asthma and Allied Conditions.[73] These new specialty organizations shared technical knowledge about the manufacture and use of the new allergy vaccines as well as the survey data about the distribution of pollinating plants. They also worked together first to plan hospitals and clinics, then to work to establish the field of allergic diseases within academic medicine.[74] They merged in 1943 to form the national allergy society for the United States and formed a specialty board for recognizing and certifying allergists under the American Board of Medical Specialties.

Immunotherapy Challenged

After 1945, the new specialists in allergy would find themselves in scientific and territorial disputes with chest physicians over asthma, with dermatologists over urticaria

and eczema, and with gastroenterologists over food allergy.[75] After 1950, as tuberculosis declined in prevalence, allergists and chest physicians in the United States would argue over almost every aspect of the treatment of patients with asthma.[76] The safety and efficacy of the allergists' immunotherapy became one of the most bitterly contested points.[77] Allergist Philip Norman, summarizing nearly a century of data on allergen immunotherapy, presented the following puzzle about its interpretation:

> Despite continued use by specialists in allergy and immunology worldwide, immunotherapy for asthma is a perennial target for criticism by nonallergists who also care for patients with asthma. Immunotherapy for hay fever, on the other hand, generates little controversy, even though the immunologic pathogenesis of hay fever is essentially identical. The reasons for this difference are not apparent from the evidence collected. Similar numbers of studies of hay fever and asthma may be found, and both find similar clinical improvement and immunologic changes.[78]

Norman was too polite to name the 'nonallergists' in question as the chest physicians who competed with allergists for the opportunity to care for asthma patients but not for those with hay fever. While allergy had become an established outpatient specialty in the United States with thousands of practitioners, in the British hospital specialist system, allergists were a small group, and the clinical practice of allergy immunization often fell to interested general practitioners. As Jackson has demonstrated, when questions arose there about allergy immunotherapy's efficacy and safety, it had only a small community of defenders to fall back on.[79] Asthma immunotherapy was much better established in the United States than in Britain, with thousands of fellowship-trained allergists. There has been a decline in the past 25 years, however, because newer non-sedating antihistamines, safer selective bronchodilators, and inhaled steroids have come to be seen as safer, simpler, and less expensive than weekly injection regimens, making it seem more convenient for patients and more cost-effective for health insurers.

Conclusions

In the early twentieth century, allergists created a dual-pronged strategy of allergy desensitization shots and manipulation of the indoor environment as a conscious alternative to climatic treatment and available pharmaceuticals. The practice of allergy and the immunologic theories that underlay it had their origins in the germ theory of disease and in the subsequent development of new theories of immunity. These beginnings shaped early theories of hay fever and asthma as diseases of infusoria, initially imagined as specific but unknown germs. It was only later that allergy came to be understood as a disease of the body's pathological response to ubiquitous stimuli such as pollens and animal danders. Even after the theories of allergy diverged from their origins in microbiology, the microscopic nature of the threat and the community of researchers continued to extend microbiological thinking into the theory and practice of allergy, borrowing both techniques of immunization and strategies of cleansing the patient's environment. While improved drugs became available in parallel with the development of allergen immunotherapy and avoidance strategies, theophylline, ephedrine, and cortisone had serious limitations both in effectiveness and safety, and were better treatments for severe manifestations of asthma than the more common symptoms of

sneezing, congestion, and itchy eyes. The everyday symptoms of allergy and asthma remained the province of the allergist and his complex schemes of allergen avoidance and immunization through the second half of the twentieth century.

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PART III
Some Tools of the Trade

CHAPTER SIX

Neutralizing Flu: 'Immunological Devices' and the Making of a Virus Disease

Michael Bresalier

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 the 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 25 per cent 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 (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 (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 organization. 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 (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

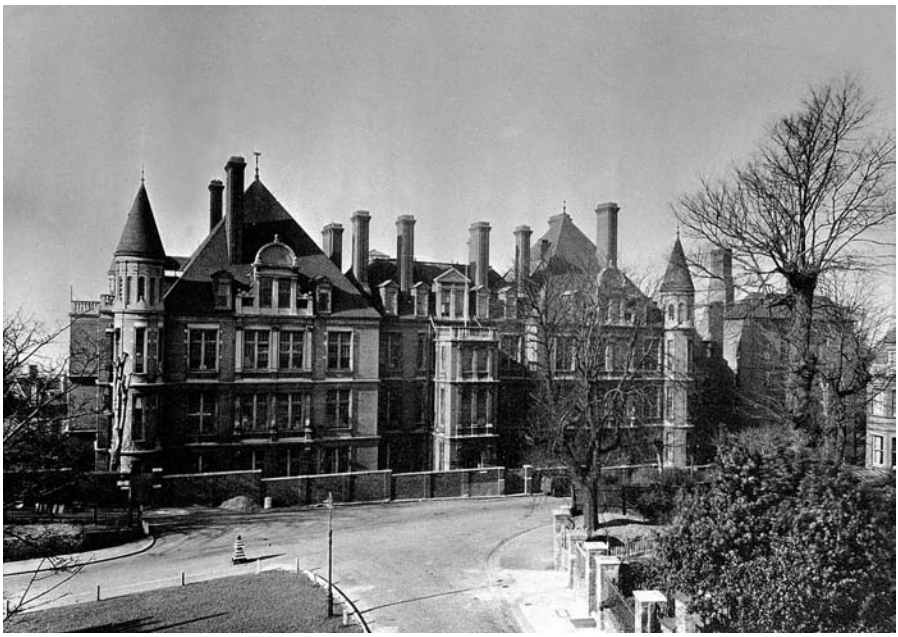

Figure 6.3 National Institute for Medical Research – Hampstead (Front View). Source: Charles Harrington, 'The work of the National Institute for Medical Research', *Proceedings of the Royal Society of London*, **136**, 1949, p. 348.

build the NIMR's expertise on established research lines. The MRC decided that the institute would 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.

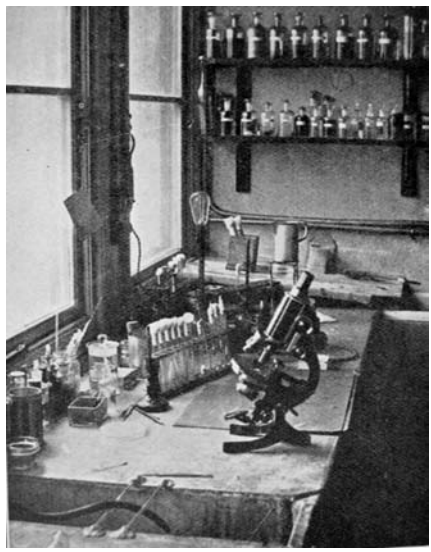

Figure 6.5 Mill Hill, Animal Hospital. Source: Laidlaw and Dunkin, *Report* …, p. 14.

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 (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 the 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 per cent 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 *pasteurien*, 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 the 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

Figure 6.7 Nasal injection of a 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.

distemper. 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 (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 that 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 (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

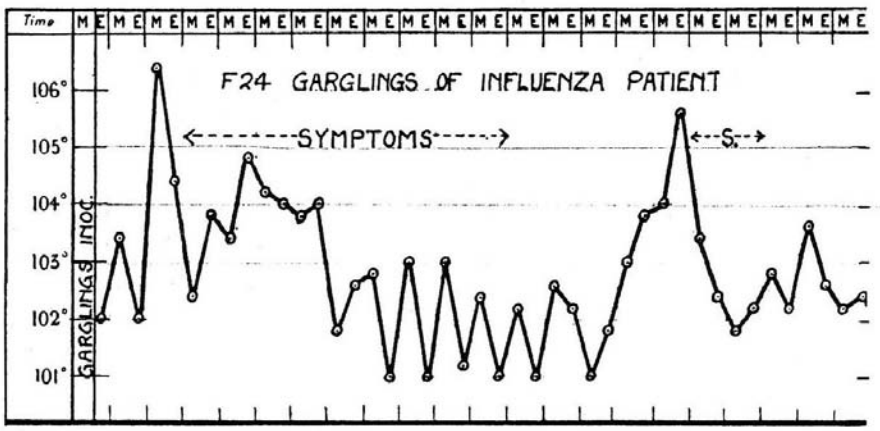

Figure 6.8 Ferret flu – fever chart. Blank fever charts, such this one used for this data, were sold at chemists such as Boots. Source: W. Smith, C.H. Andrewes, and P.P. Laidlaw, 'A Virus Obtained from Influenza Patients', *Lancet*, **2**, 1933, p. 67.

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

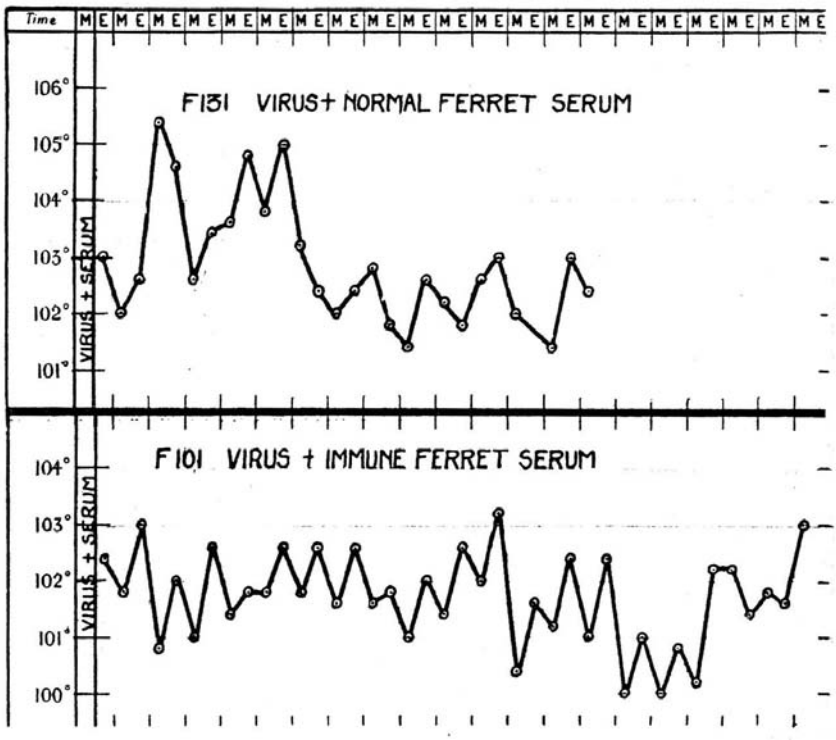

Figure 6.9 Ferret flu – neutralized. Upper chart – Ferret (F131) infected with a mixture of virus and normal ferret serum. Lower chart - Ferret (F101) infected with a mixture of virus and immune ferret serum. Virus neutralization is demonstrated in the lower chart. Source: W. Smith, C.H. Andrewes, and 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 and 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 the 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

I, FRIDAY, JULY 7, 1933

COMPETITIONS IN NEWSPAPERS

POLICE WARNING TO LONDON PRESS

The subject of newspaper competitions was again raised in the House of Commons last night.

On the motion for the adjournment Mr. Pike (C., Attercliffe) referred to the prosecution of the "Sheffield Telegraph" and "Sheffield Independent" for publishing advertisements of competitions on the result of the Derby.

He recalled the questions he had already put to the Home Secretary on this matter, and said: My object in raising this matter on the adjournment is as far as possible to bring to the notice of the Home Secretary the existence of these acts of illegality according to the Betting Acts by papers operating in the area of Sheffield, but published by a company whose headquarters are in London.

"If the Chief Constable of Sheffield is, as the Home Secretary stated yesterday he was, entirely responsible for putting into force the Betting Act of 1853 in respect of the publication of advertisements by lottery, it appears from that act that that authority is actually the Town Clerk of Sheffield, who is, I understand, a lawyer.

"If the Chief Constable of Sheffield is in any difficulty in regard to instituting proceedings against other newspapers he must seek the advice of the Town Clerk, who is the local adviser to the Corporation.

"As far as I can gather, the authority of the Town Clerk of Sheffield on the question of any jurisdiction which the Chief Constable might have in instituting proceedings against these papers will be the Betting Act of 1853.

"The object of my rising to-night is to seek from the Home Secretary information of how it is possible to bring within the law those papers which are guilty in the eyes of the law of precisely the same offence against the law for which the "Sheffield Daily Telegraph" and the "Sheffield Independent" have been fined.

"They have been fined for using premises situated in Sheffield for the purpose of betting and receiving moneys by undertaking to pay money on certain contingencies relating to horse races.

UNFAIR DISCRIMINATION

"We do not object to having been fined for that purpose, nor do the newspapers object to having been taken, not as a test case, but as an example of what the law can do.

"But what we do object to is being selected for prosecution—because this is not the first occasion on which the Sheffield Daily Telegraph' and the Sheffield Daily Independent' have been selected—when other newspapers are guilty of the same offence within precisely the same area.

"If one paper is to be continually apprehended for an offence, it seems to me a very grave injustice that other newspapers circulating within that area can defy the law with absolute impunity. I object to a legal anomaly which enables the Chief Constable of Sheffield to prosecute Sheffield newspapers, but which apparently denies him the right to prosecute the London newspapers which are operating in the same area.

"A London paper, it appears, can set up an office in Sheffield, collect its news in Sheffield, control its distribution in that area and advertise in that area details relative to lotteries, and send those papers to those who enter into those competitions.

"It appears to me that it is time that some greater distinction were placed upon the meaning of the Betting Acts so that the Sheffield and other Chief Constables who are administering this law can know exactly to which authority they can appeal and when action can be taken.

40 YEARS' SEARCH FOR CAUSE OF INFLUENZA

HOW THE VIRUS WAS TRACKED DOWN

WORK IN BRITISH LABORATORIES

FROM A MEDICAL CORRESPONDENT

The story of the search for the cause of influenza, which, as reported on Page Thirteen, is now believed to be nearing success, goes back to 1892. In that year Prof. Pfeiffer, in Berlin, made the observation that a certain small bacillus was, in his experience, constantly associated with the disease. The micro-organism was small and delicate; at first there was difficulty in cultivating it, but this difficulty was overcome when it was found that the organism has a liking for blood.

Pfeiffer gave it the name Bacillus influenzæ, and whatever the ultimate truth of the causation of influenza may be, it is certain that this name must be retained.

DR. LAIDLAW.

If the microbe is found, for example, in parts of the body such as the mouth or alimentary canal, where normally there is a rich flora of harmless germs, it is always possible that, under the circumstances provided by the organism usually produce the symptoms reinoculate a second and first, and so on in series.

With bacillus influenzæ been possible to do this animals appear to be refra proof, the cause remains blood-loving microbe of P nevertheless obtained.

Nevertheless, interest did not wane. It was fo bacid, that bacillus influen in the nose and throat of and that in small epid catarrh the organism numerous numbers. On small outbreaks, the " fluenza, it is sometimes the organism at all.

VIRUS THEORY A

During the world epid

Now, how can it be proved that an organism is the cause of a disease? The occurrence in large numbers of a particular microbe in a case of a disease does not mean necessarily that this microbe is the true cause; judgment on such a point is governed by many considerations.

ANIMALS NOT SUS

The difficulty of elim eliminated when it is po animals with the suspect

Now here comes the revealing, reconciling observation: whilst a pig infected either with virus or bacillus influenzæ became but slightly ill and always recovered, a pig infected with both virus and microbe became seriously ill and usually died.

Further, the disease caused by the mixture of virus and microbe spreads to other normal healthy pigs by mere contact. The contagiousness of the full-blown disease is the counterpart of influenza in man.

These discoveries in America naturally attracted the attention of bacteriologists in other countries and gave rise to a cautious optimism. It remained uncertain how far Shope had been dealing with human influenza virus or merely with an analogous disease of a domestic animal.

THE FINAL STAGE

through a recent attack of influenza, can be infected with bacteria-free filtrates.

But this interpretation is open to the criticism that positive results with human subjects are fictitious; that the infection in other words, which follows the spraying has developed naturally. Many attempts to answer such a criticism were made, but none was entirely satisfactory.

Research, then, after the last great epidemic, had failed to solve this really important problem. Both theories—Pfeiffer's and the virus theory—had their supporters, but neither met with general acceptance.

The practical outlook was gloomy. Vast epidemics might sweep the world again and mankind would again be the helpless victim of the spreading scourge.

BACILLUS PLUS VIRUS

Several years ago, during a then influenza outbreak in America, Dr. Shope, of the Rockefeller Institute, studied an epidemic of fever which occurred in swine. Shope found that the disease was readily transmissible by spraying with filtrates, but the infection thus provoked was milder than the naturally occurring disease.

This observation lent support to the belief that a filterable virus is the real cause, at any rate, of swine influenza. But he found also that pigs which died of the natural disease were affected also by a small blood-loving microbe similar to that described by Pfeiffer.

THE DAILY TELEGRAPH, FRIDAY, JULY 7, 1933

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DELEGATES' DAY OF DOUBT

TO PACK OR NOT TO PACK?

DEPARTURE PLANS CANCELLED

To pack or not to pack? That was the question agitating most of the delegates to the World Conference and their staffs yesterday.

For the moment international monetary and economic problems were forgotten. Delegates ceased to be national mouthpieces and became just harassed individuals. Americans, Frenchmen, Germans, Italians, Japanese—representatives, in fact, of all the sixty-six nations at the Conference—stood thinking of station, physiognomy and output restrictions. They thought instead of steamer passages, train reservations, the settlement of hotel bills, the collection of belongings, the stopping of letters at the Conference headquarters, the packing up of documents, the arrangement of private farewells and of the many invitations they had accepted.

THREATENED ENGAGEMENTS

Much hospitality has been shown to the delegates, but much more had been planned, and it was realized that many engagements would have to be broken if the Conference came to an end.

Many delegates had planned to visit the Royal Show at Derby to-day. Their programme for the coming days included receptions by Gen. Smuts and Lady Bell, visits to the Port of London Authority, the Admiralty Establishments at Rosyth, the White City and the Boy Scouts' training centre at Chingford, a garden party at Rastrick and a gala presentation of Brutus, Bart.

Eager to know whether they were going home or not, the delegates thronged the Conference headquarters yesterday, waiting while their fate was decided by the Bureau. It was a strange scene. The headquarters from that of most days.

The Conference hall was deserted, no names of speakers appeared on the green boards, no red and blue lights twinkled in and out, no division bells rang. Instead the delegates stood about idly waiting for the verdict of the Bureau, which was sitting in an out-of-the-way room.

DRAMATIC CHANGE

At the beginning of the day sent until late in the afternoon very few thought that the Conference would continue. Arrangements were, in fact, made to send back the League of Nations' staff to Geneva to-morrow.

Then, at the end of the day, the uncertainty was removed. The Conference was changed instantly.

Plans for departure were abruptly brought to an end. Delegates resumed their normal demeanour. Officials calmed their fears. Journalists from all over the world settled down to another long week of work. The Office of Works ceased to speculate over what was to happen to the Geological Museum, arrangements for a special wagon, to convey all the documents of the League of Nations to Geneva under seal were cancelled. The Conference had been saved. Partially at least.

Picture on Page Sixteen.

PRIMARY CAUSE OF 'FLU ISOLATED

A FILTER-PASSING VIRUS

ANIMALS RENDERED IMMUNE

BRITISH DOCTORS' DISCOVERY

That the primary cause of influenza is a filter-passing virus is the conclusion reached as a result of striking experiments carried out by three British doctors—Dr. Wilson Smith, Dr. C. H. Andrewes, and Dr. P. P. Laidlaw—at the National Institute for Medical Research and described by them in to-morrow's issue of the "Lancet."

They discovered that ferrets, which were used for the first time in this line of research, are susceptible to infection with human influenza. In this way the virus of the disease was isolated.

It was also found that ferrets which had recovered from the disease were thereafter immune from it, and that the serum of human convalescents was capable of neutralising the virus of the ferret disease.

A medical correspondent, in the article which appears on Page Ten, regards these discoveries as of the greatest importance. He suggests that their significance, in combination with results recently arrived at in America, may well be that mankind will not again find itself a helpless victim to a great influenza epidemic.

OBJECTS OF ART FOR THE QUEEN

BEQUESTS BY LADY MOUNT STEPHEN

Wills passed for probate yesterday reported on Page Fifteen disclosed the names of sixteen women, the combined value of whose estates exceeded £911,000.

The most notable was that of Lady Mount Stephen, widow of the first president of the Canadian Pacific Railway, who left gross estate of £196,218, with net personalty £185,527.

Lady Mount Stephen, who was on terms of personal friendship with the Queen (for many years she was lady-in-waiting to the "Duchess of Teck"), has bequeathed to her Majesty a number of portraits and objects of art of historical interest.

Bequests were also made to the

The Daily Telegraph

During the month of June the average net sales of THE DAILY TELEGRAPH *as certified in the auditors' certificate amounted to*

325,573

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Throughout the steady progress of the last three years, from 100,000 copies per week to the present figure, THE DAILY TELEGRAPH *has safeguarded consistently for its advertisers that valuable asset, reader-interest. It has gained new readers solely through the traditional values of good journalism and news service.*

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HARVEY, MONK & CO.,
Chartered Accountants.

London, July 4, 1933.

NAZI THREAT TO FRANZ LEHAR

BOYCOTT OF ALL HIS COMPOSITIONS

FROM OUR OWN CORRESPONDENT

VIENNA, Thursday.

Franz Lehar, the famous composer of "The Merry Widow" and many other operettas, who can be described as Vienna's most beloved musical personality, is threatened through the Nazi Press agency with the boycott of his compositions in Germany.

Franz Lehar is alleged to have said in private conversation that the invasion of Belgium by Germany in 1914 was a breach of the treaty, and the boycott is a punishment for this alleged expression of opinion.

Franz Lehar said to-night: "It is quite untrue that I made the remark attributed to me. I was not even present at the meeting of the Society of Authors in Vienna when the remark was made.

Figure 6.10 Discovery of flu virus. 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 per cent (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 installations 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

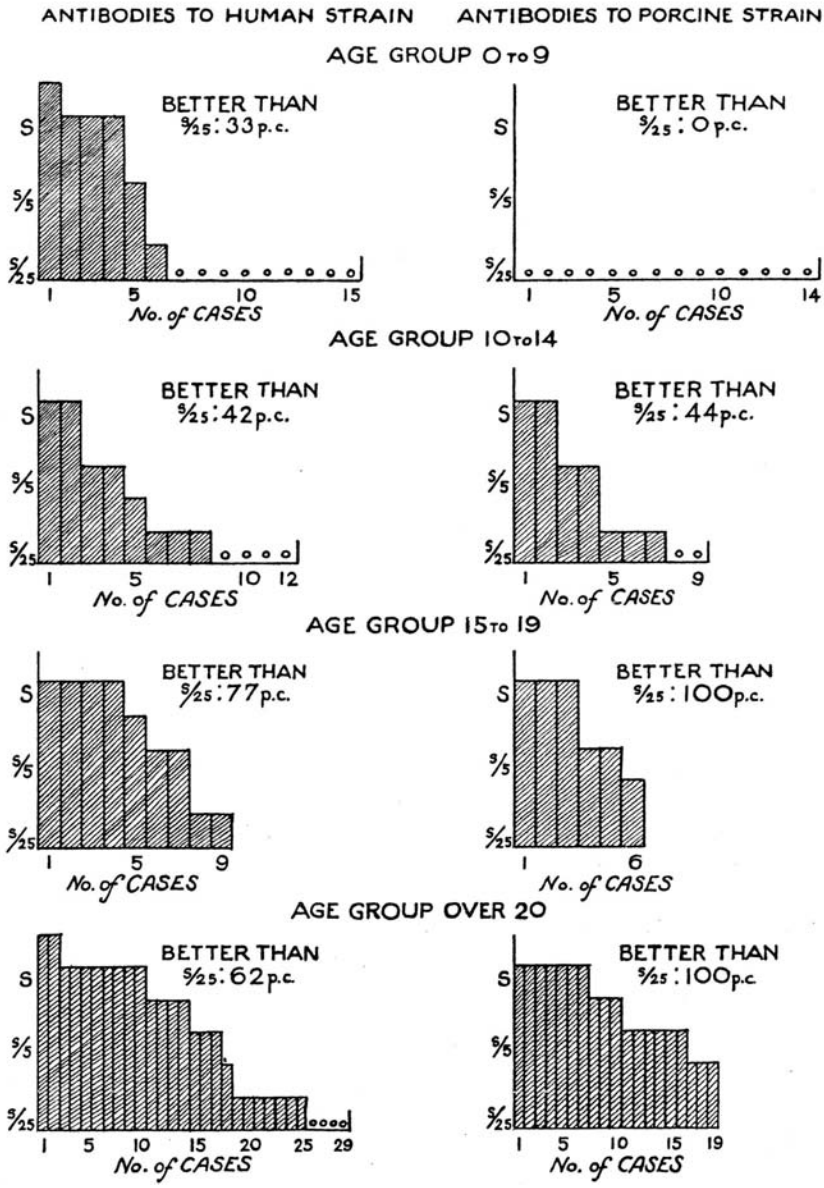

Figure 6.12 Neutralizing antibody levels in Londoners. Each vertical column represents a serum. The height of shading indicates the quantity of antibody in the serum. Sera were graded as better than S (standard IH2 or IH4 horse-antiserum), equal S, S/5 (one-fifth the neutralizing power of S), or S/25 (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 officials 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

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CHAPTER SEVEN

Creatures of Reason? Picturing Viruses at the Pasteur Institute during the 1920s

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When considered as part of a history of disease, immunity cuts a rather strange figure. As experience, it cuts no figure at all; its presence can be inferred only when an infectious challenge fails. Immunity is thus the result of reasoning about disease's absence. It is a sort of shadow figure whose shape is determined by medicine's focal point of interest, disease. As the object of the scientific field of immunology, immunity has been rendered visible in a variety of ways. Late-nineteenth-century bacteriology set the stage by linking the progress of medicine to the relentless expansion of the concept of specificity. Infectious diseases, like the microbes that caused them, came in species. Before bacteriology, as Andrea Rusnock's examination of Jenner's work in this volume clearly demonstrates, natural historical classification of disease symptoms across and within species could and did function effectively as explanation. But, beginning in the 1860s, medical science began to revolve around a repeated series of routines in the bacteriological laboratory. Extraction, filtration, cultivation, and inoculation produced cultures of microbes of considerable purity, which could then be viewed with light microscopes and their associated technologies of stains and filters. Microbes and the diseases they caused became natural and more-or-less stable kinds of things in large part because they could be identified morphologically. Illustrations taken from bacteriological textbooks of the period testify to this interrelationship between the processes of producing objects and visualizing their specific shapes.[1]

Of course, unlike the organisms traditionally handled by natural historians, diseases were, first and foremost, experiences, not objects. As Georges Canguilhem suggested (and as Moira Howes demonstrates in her analysis of pregnancy immunology in this volume), medical understanding of physiological norms tends to begin with pathology. A corollary of this claim is that microbes were of medical interest only insofar as they could be manipulated in the hopes of finding a way to eliminate or control the diseases they caused.[2] To be truly effective, therapies such as vaccinations and serotherapy had to be firmly grounded in these practices of specificity. Likewise, public health measures controlling water supply, drainage, sewage or quarantine should, whenever possible, rest upon the authority of the visual identification of the microbial culprit. But experience, too, was beginning to be restructured by 1900. The expanding use of the X ray was merely the most spectacular example of how mechanically and procedurally-generated visual signs became surrogates for patients' symptoms. Punch cards, rubber stamps,

charts and graphs played an equally important role in the rationalization of the new focal point of scientific medicine, the hospital.[3] Over the next few decades, hospital-based care, public health, and laboratory-based medicine increasingly converged around a common mandate of increasing and standardizing inscriptions.

Ideals of specificity, however, were quickly extended beyond the realm of what could be rendered visible with the light microscope. Robert Koch, a clinician trained as a naturalist, had once claimed the smallest morphological differences among the *Vibrio* types as proof they were distinct species. His students, however, began to make inferences about immunity at the sub-microscopic level. Richard Pfeiffer, for example, relied on cross-immunity experiments to mount claims about the specificity of the immune response. The serum of guinea pigs immunized against one strain of cholera *Vibrio*, he argued, would cause only that strain to form clumps that could be seen *in vitro*.[4] Less than a decade later, Paul Ehrlich's diagrammatic illustrations of his immunological theory pursued this same direction to its very limit. Where Metchnikoff, who, like Koch, had trained as a naturalist, claimed inspiration for his phagocytic theory of immunity from actually seeing the cells of a starfish larva digest other cells, Ehrlich's graphical depiction of his side-chain theory lacked any explicit links to the shapes of the utterly invisible entities they claimed to represent. In a reversal of post-Vesalian anatomical practice, Ehrlich's images represented function, with little or no regard for structure. These illustrations also functioned, as a now-classic analysis suggests, as both an intellectual heuristic and as an organizing principle for orchestrating laboratory work.[5] They were also a point of conflict, as immunological imagery was itself fast becoming a framework for debates in the field. Pfeiffer's critics, many of them dedicated to Carl Nägeli's views regarding the continuum of natural forms, derided his claim to having observed specificity, or at least its consequences, in a test tube. Ehrlich's foray into the graphic arts was received by some positivist French biologists (like Félix le Dantec) as a dangerous epistemological crutch that would reify immunological entities whose existence remained speculative. I have no direct evidence of this, but I suspect the prominent cadre of Parisian intellectuals championing the phenomenological analysis of philosopher Henri Bergson would have been delighted with these developments. Bergson never hesitated to graphically depict experiences like that of memory as a sort of visual counterpoint to the project of brain localization he so relentlessly critiqued.[6] And we should keep in mind how, according to Bergson's critics, 'Bergsonisme' had infiltrated public education in the Third Republic by the first decade of the twentieth century.[7]

In any event, the fascination with the very large functional responses that could be elicited from very small doses of antigen were accelerated in the wake of Richet and Portier's 1902 discovery of anaphylaxis. Richet later argued that this discovery would transform organ-based physiology into a 'Chemistry of Imponderables' dominated by the study of reactions, not structures.[8] At exactly the same time, a new class of entities, filterable viruses, were entering the field of medical research. Despite their invisibility, their status as infectious pathogens had become unquestionable. In the inaugural issue of the Pasteur Institute's *Bulletin*, Emile Roux listed ten infectious diseases that had been added to their ranks since 1898.[9] Offering a cursory history of these new objects, Roux declared that filterable viruses, once mere 'creatures of reason' derived from Pasteur's speculations about the cause of rabies, were changing, as investigators had now

'given them a reality' they formerly lacked.[10] Despite viruses' continued resistance to visual inspection, Roux, who would become Director of the Institute in 1905 following Duclaux's death the preceding year, was nonetheless sanguine about the prospects for progress in the field. All that was required were consistent statements regarding the conditions under which these entities passed through the filters that held back other bacteria. What grade of filter was used? Was it submerged in growth media? How was the porosity of the filter established? What pressure was used, and for how long? So long as such issues were explicitly identified, Roux thought there was little need of addressing the very slight possibility that conventional microscopy could somehow be improved to visualize these entities, whose size, he despaired, bordered 'the length of a wave of light'.[11]

As Angela Creager has shown in her study of Wendell Stanley's work on Tobacco Mosaic Virus, not everyone followed Roux's line of reasoning. Stanley's work represented a strain of investigation at the Rockefeller Institute for Medical Research that explicitly adopted chemical approaches over bacteriological ones in the study of viruses.[12] The somewhat paradoxical consequence of this was that these two seemingly divergent strategies converged around the goal of inventing a way of generating a reliable image of the entity under investigation, be it through the processes of culturation and staining, or precipitation and crystallization. Echoing a Kochian approach to bacteriology, the aim of imaging the macromolecule that was TMV was part and parcel of adopting TMV as an experimental model for the study of viruses. But other investigational strategies were available, both during the 1920s and in the decades that followed. Under the rubric of 'unmasking' a virus thought responsible for cancer, Creager and Jean-Paul Gaudillière have identified three distinct 'modes of visualization'; namely, the pathological, macromolecular, and the molecular genetic.[13] Each involved a unique, but sometimes overlapping, array of images, including those distilled from histological sections, ultracentrifuge sedimentation results, viral particle counts, and cell cultures. Because cancer was not at this time conceptualized as a 'contagious scourge', the images and the experimental arrangements that generated them had to perform a double duty. They not only had to picture the virus itself (or at least work towards such a goal), they also had to depict the virus as the cause of what was slowly revealing itself as one of great epidemics of the twentieth century.

To this brief taxonomy, I would like to add a fourth approach, which I will call 'natural historical'. As already mentioned, Jenner's work provides an excellent example of how this sort of reasoning was deployed to explain infection before the dominance of laboratory-based bacteriology. But as an experimentally-generated strategy of visualization, the natural historical mode seems to have persisted well into the twentieth century, at least in the case of epidemic encephalitis. The unusual status of the disease in question should not go unnoticed. Unlike smallpox or cancer, *Encephalitis lethargica* was widely perceived as a novel epidemic disease.[14] Yet the nature of the disease and its mechanism of transmission proved extraordinarily confusing to the dozens of researchers that took up its study during the 1920s. Indeed, such questions remained unresolved by the time the epidemic forms of encephalitis disappeared by the 1930s. Thus, in addition to the fundamental controversies over what, exactly, filterable viruses were, encephalitis researchers were confronted with the additional challenge of demonstrating that their new object was both coherent and robust. It was coherent,

proponents argued, in the sense that epidemic encephalitis was a disease *sui generis*, and not a mere collection of essentially unrelated symptoms; and it was robust, in the sense that its study could shed light on the nature of viral epidemics in general. A small but influential group of American neurologists centered in New York City worked hard to deploy their encephalitis research around both issues. They did so, in part, to further their professional interests.[15]

Across the Atlantic, a *pasteurien*, Constantin Levaditi (1874–1953) adopted a very different tack. While some American neurologists embraced encephalitis as a model disease that could help extend their field's scientific authority in the domain of public health, Levaditi's interests were elsewhere. Unlike neurology, the investigative fields Levaditi worked in – cellular pathology and immunology – had already been incorporated into the very bedrock of public health by the time encephalitis first appeared. Following Roux's lead, Levaditi's efforts were thus focused on framing encephalitis as a problem that could be managed by the conventional strategies of scientific medicine, in spite of the fact that filterable viruses were invisible. His solution was to make them visible by adapting natural-historical methods to the practices of the bacteriological laboratory. The very definition of a virus changed in the process, as Levaditi began to visualize them as temporal, rather than morphological, objects. In tracing the transformation of these strategies from their initial static and iconic mode to a diachronic form of presentation, I will argue that Levaditi's natural-historical approach evolved out of his empirical work with a number of viruses. Despite the fact that his efforts to group together viruses around family resemblances appear to be yet another strain of the nostalgic holism witnessed in other fields of biomedicine, I argue that this is not the case. Levaditi's efforts bore only a superficial resemblance to more thorough-going critiques of medical reductionism then proffered by some clinicians and epidemiologists.[16] Although Levaditi's work did not exploit any of the physico-chemical methods and technologies that were then coming into play, his work nonetheless adapted the latest biological tools, in the form of the successful viral passages recently made of the virus causing herpes. Levaditi's work in this domain was, I suggest, 'craftlike', in the sense that its success relied heavily upon the idiosyncratic skills of the investigator framing the argument, rather than the creation of a rationalized and automated means of generating novelty that eventually came to dominate virology and immunology in the second half of the twentieth century.[17]

Picturing Epidemic Encephalitis as a Viral Disease

Roux's insistence that viruses had moved into the domain of real things without having been visualized is perhaps unsurprising, given the context of the times. Morphology and specificity were closely related, and the first decades of the twentieth century witnessed some outspoken skepticism regarding the utility of specificity to biomedicine. Anaphylactic shock and serum sickness threatened to undermine the utility of vaccine and serum therapy. The specificity of the Wassermann reaction, the most important diagnostic test for syphilis, was in dispute.[18] The epidemiology of poliomyelitis and typhoid indicated that a person could be completely asymptomatic, yet harbour and spread the microbe responsible for these diseases, thus rendering traditional methods of clinical diagnosis suspect. In response, many clinicians and epidemiologists revived the non-specific, neo-Hippocratic theory of 'epidemic constitutions', with its clinical

correlate, 'constitutional' medicine, which emphasized individual variation as a contributing factor to disease. The Liverpool clinician, Francis Graham Crookshank, advanced precisely this argument when he declared that medicine was no longer 'an exact science' in a 1923 essay.[19] The study of bacterial variation emerged as a viable research program during the same period.[20] In some instances, the visual project of classical bacteriology actually seemed to be operating in reverse, as the influenza pandemics of 1918–20 destabilized the claim that Pfeiffer's bacillus was responsible for the disease.[21] And, in contrast to viruses' continued invisibility, the visibility of 'filterable virus diseases' was on the rise. By 1926, Thomas Rivers, a bacteriologist at the Rockefeller Institute, was able to list sixty-five such diseases.[22]

Particularly disturbing to some bacteriologists was the notion that some of these viral diseases were entirely new clinical entities. Such was the case with *Encephalitis lethargica*, a neurological disease first named by Constantin von Economo, a Viennese neuroanatomist, in 1917. Within three years, the disease, popularly (and erroneously) known as 'sleeping sickness', had assumed an epidemic form across Europe and North America. Its symptoms were protean. In its acute form, it frequently resembled influenza. But its chronic form could include depression, headache, psychosis, eye tremor, delirium, convulsions, and, most significantly, extreme lethargy, or even its inverse, insomnia. But, despite the nearly five thousand biomedical articles that had been published on the topic by 1929, there was little consensus regarding either the disease's symptomatology, or its aetiology.[23] Encephalitis' epidemic profile, which resembled that of polio, suggested that it must be an infectious disease caused by a filterable virus. But, unlike polio, encephalitis proved almost impossible to transmit to experimental animals.

One of the most enduring reports of successful transmission, however, had been reported by Constantin Levaditi, a Rumanian-born bacteriologist who began working out of the Pasteur Institute in Paris in 1900.[24] On the heels of an announcement by the Parisian clinician and hygenist, Arnold Netter (1855–1936), that there were probably more than 10,000 cases of encephalitis in France at the time (almost all of them undiagnosed), Levaditi published his first study of encephalitis in 1920.[25] In this paper, Levaditi utilized the standard visual conventions of cellular pathology of the day, providing in his publications (for example) a series of illustrated plates that demonstrated the presence of 'inclusion bodies', a cellular modification that was thought to signify the activity of a filterable virus.[26] Picturing such entities was itself a matter of interpretation. Several of the images preserved in his archives at the Pasteur Institute, for example, feature pre-publication drafts that include instructions at the bottom of the image to the illustrator to increase the size of the 'granulations' in several of the drawings (see Figure 7.1).[27]

But, by the time of his next major publication of early 1922, Levaditi had developed an entirely new visual system in addition to the standard array of hand-drawn colour plates of pathological tissues and photographs of dermal reactions in patients and animals that then served to create a form of 'virtual witnessing' in bacteriological investigation.[28] The system in question combined a series of standardized icons, some of which Levaditi had already deployed in earlier papers, that were now set within the temporal framework of a pedigree (see Figure 7.2).

This 'icono-temporal' approach allowed Levaditi to present the transitory and invisible dynamism of a group of viruses, rather than simply reproducing the effects of

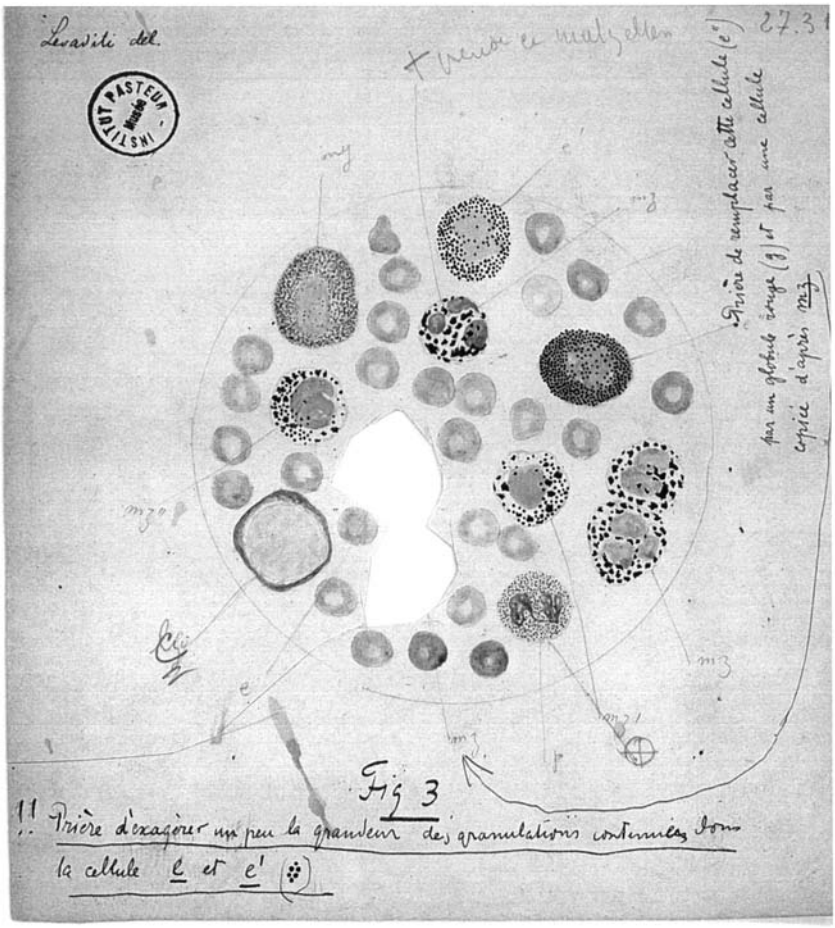

Figure 7.1 A draft illustration from Levaditi's laboratory, with a request for alterations. Source: Constantin Levaditi archives at the Pasteur Institute, Paris. FR IP LEV 03, item 27.31, n.d.

viral disease witnessed by the experimenter at the macro- and microscopic levels. That is to say, he tried to visualize a family of biomedical entities whose invisibility was due not only to their miniscule size, but also to their transformative nature.

Levaditi's system was not entirely unique among bacteriologists in general, or encephalitis investigators in particular. The particular set of icons he used, which variously represented brain, spinal, dermal and other tissues, as well as different species of experimental animals, appear to have been limited to publications emerging from his laboratory at the Pasteur Institute (see Figure 7.3). But a few other researchers used similar tools to depict, for example, the relative sizes of tumors subjected to antisera or physical treatment.[29] Pedigrees, on the other hand, had been common currency for eugenists and their publics since around 1900, though they tended to represent different facts about inheritance for their British, American, and German readers.[30] To judge by an admittedly limited survey of the pages of the *Journal of Experimental Medicine*, it

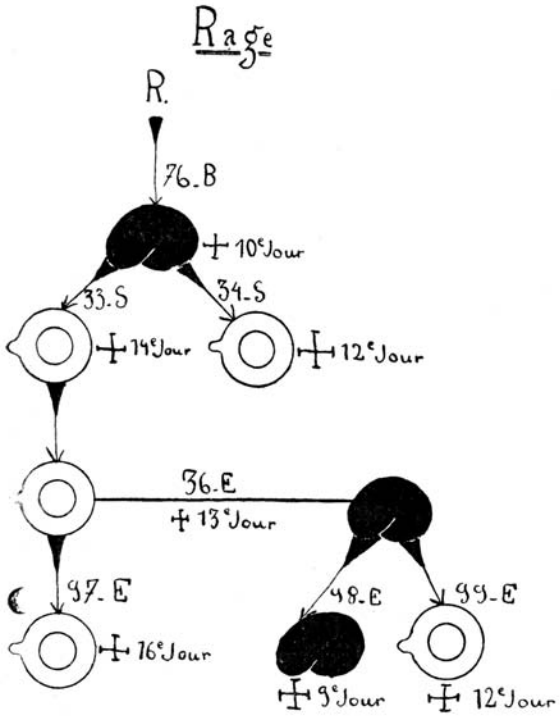

Figure 7.2 A pedigree of a strain (R) of rabies in Levaditi's laboratory. The virus was injected into animal 76.B (the animal died 10 days later), and was then transmitted to two animals (33.S and 34.S) – both of which died within two weeks, with no symptoms of corneal inflammation. After the strain was passed again through animal 36.E, infectious material was then taken from its (asymptomatic and unshaded) cornea and (symptomatic and shaded) cerebrum, and passed through three different animals (97.E, 48.E and 99.E). Source: C. Levaditi, P. Havier, and S. Nicolau, 'Étude expérimentale de l'encéphalite dite "léthargique"', *Annales. Institut Pasteur*, **36**, 1922, pp. 63–104 and 105–48 at p. 138.

would appear that, in the American context, some bacteriologists interested in filterable viruses adopted the pedigree around the same time as Levaditi. One group of researchers at Tulane University in New Orleans, for example, routinely used pedigrees during the early 1920s to depict their success (or lack thereof) in serially transmitting the viruses of measles and dengue fever to various species of experimental animal.[31] Others did the same with yellow fever.[32]

These researchers, however, were working with diseases that were well-established as clinical entities. Their goal was to convert them into laboratory objects by establishing a manageable animal reservoir for the virus thought responsible for the disease, with the ultimate goal of successful antisera or vaccine production. Their pedigrees served to illustrate the success or failure of their particular model, and little else. The virus in question, like a 'degenerative trait' for the eugenists, either persisted in the 'offspring' at the end of the pedigreee, or it did not. A handful of other investigators, however, utilized this same visual form to illustrate the nature of viruses in general, rather than

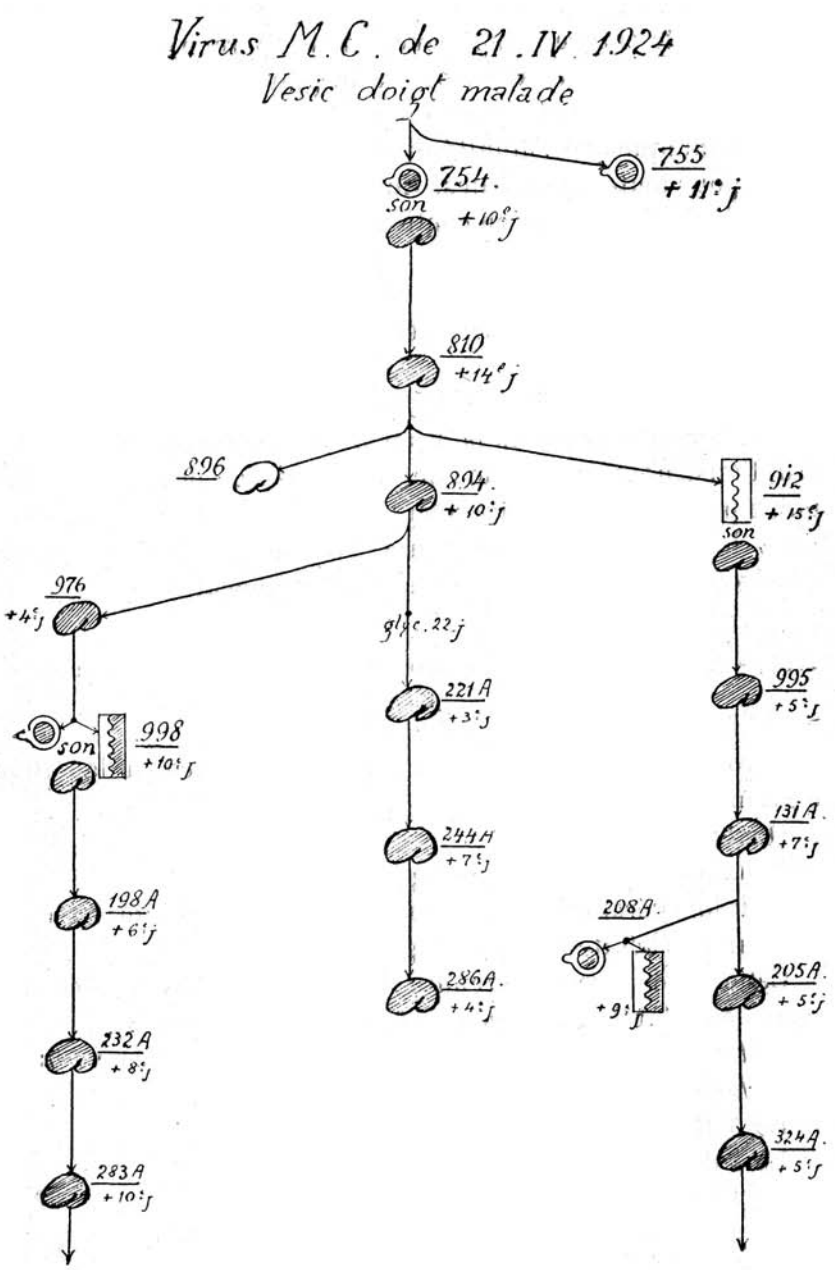

Figure 7.3 A graphical depiction of a strain of herpes virus (M.C.), showing its varying ability to generate symptoms in corneal, cerebral, and dermal tissue. Note the lack of symptoms in the cerebrum of animal 896, while this same strain proved capable of generating cerebral (and, sometimes, dermal) symptoms in the animals following 912 and 976. Souce: S. Nicolau and P. Poincloux, 'Étude clinique et expérimentale d'un cas d'herpès récidivant du doigt', *Annales. Institut Pasteur*, **38**, 1924, pp. 977–1001 at p. 989.

any one disease in particular. Their pedigrees were tools that forcefully put forward ideas about family resemblances between viral diseases. One such bacteriologist, Thomas Rivers, was, like Levaditi, searching for investigative tools that would allow him to create a classificatory system of viral diseases that was based on an amalgam of clinical and experimental evidence. In a 1923 paper, for example, Rivers and his co-worker, William Tillett, cited Levaditi's recent investigations into epidemic encephalitis with approval, and then went on to offer a pedigree of their own, showing how the Varicella virus could be passed through rabbits.[33] The chart was accompanied by a table offering an initial classification of virus groups – quite unlike Roux's 1902 paper, which offered only a list of viral diseases more or less in the order in which they had been identified as such. Upon discovering that his colleagues at the Rockefeller Hospital had successfully generated the same set of varicella symptoms in rabbits by passing infectious material taken from rheumatic fever patients, Rivers and Tillett quickly retracted their intimation that they had successfully isolated the Varicella virus. In the same paper, they renamed the mysterious entity 'Virus III', and illustrated their method of producing this formerly-unknown disease of rabbits with yet another pedigree.[34] Rivers continued to deploy pedigrees in some of his published virus research while also attempting to develop a coherent grouping of viral diseases.[35] The latter work eventually emerged as his landmark 1927 review.[36]

While Rivers continued to work on viruses that were often, like Virus III, experimental tools at some remove from pressing clinical problems, the issue of epidemic encephalitis was very much in the hands of the Rockefeller Institute's director, Simon Flexner. Flexner's minimalist visual approach (he rarely published with diagrams) was rather different from that of either Rivers or Levaditi, and might be described as 'indexical', in the sense that American philosopher Charles Sanders Peirce implied in 1885: 'The index asserts nothing; it only says "There!" It takes hold of our eyes, as it were, and forcibly directs them to a particular object, and there it stops'.[37] Like most mainstream bacteriologists, Flexner believed in the specificity of epidemic encephalitis, and his visual strategies generally reflected this. Stacks and stacks of index cards featuring nothing but written descriptions of procedures and reactions between numbered viral strains of various diseases and the experimental animals that suffered their injections populate Flexner's archive (see Figure 7.4). Film was occasionally used in an attempt to articulate an animal's reactions over time (see Figure 7.5), but these were merely an experimental analogue of the clinical observation of neurological disease with motor effects, the study of which was also beginning to incorporate cinematic techniques (see Figure 7.6).[38] As far as encephalitis was concerned, every instance pointed to failure. Despite having easy access to what was probably the largest pool of encephalitis patients in the world in New York City, Flexner and his co-workers (usually Harold L. Amoss) failed to achieve serial transmission of supposedly infectious material taken from patients.

Herpes as Symptom and Explanation

Levaditi, on the other hand, insisted that similar problems encountered in his own laboratory illuminated the true transformative nature of the encephalitis virus. Like polio, vaccinia, smallpox, herpes and rabies, encephalitis was part of a 'family' of infectious diseases he eventually dubbed the 'neurotropic ectodermatosis group' (see Figure 7.7).

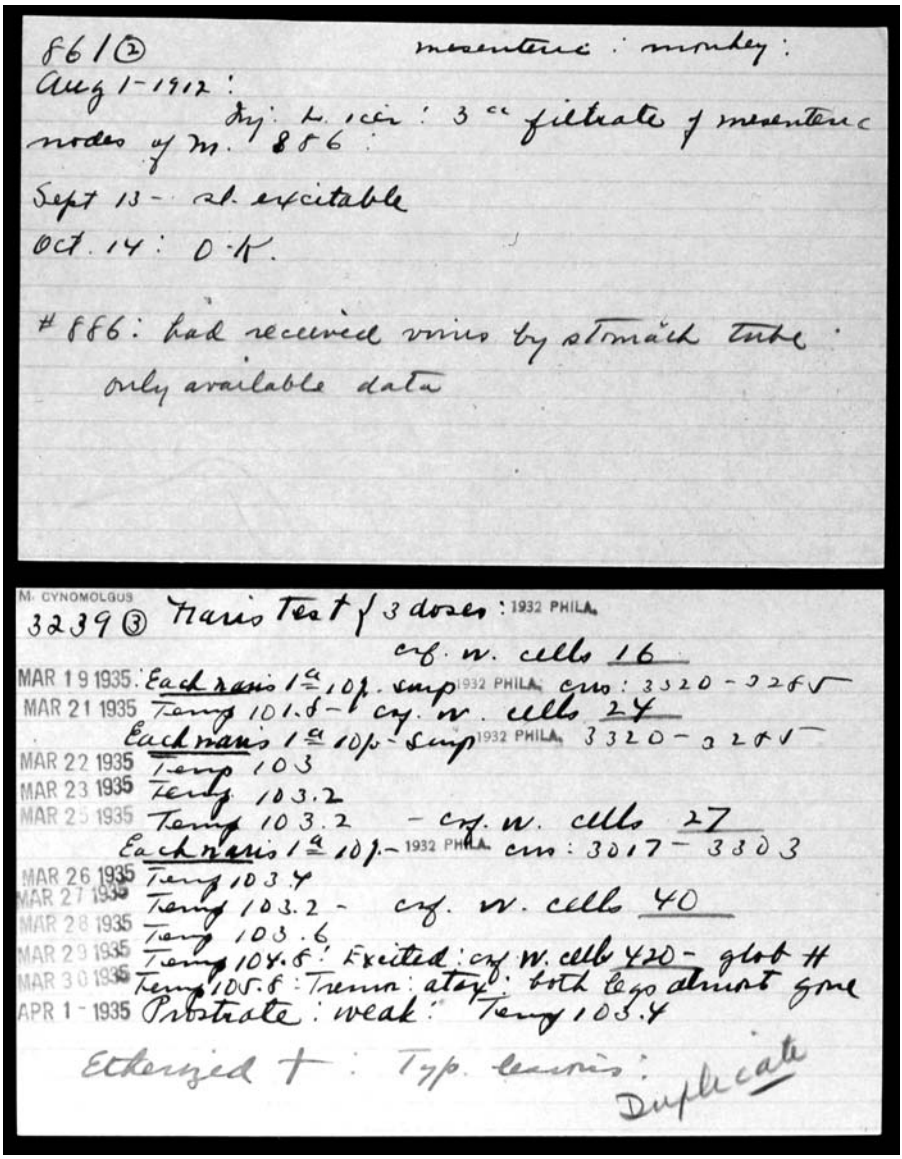

Figure 7.4 Two index cards outlining experimental procedures ('received virus by stomach tube'), symptomatic observations ('Temp 105.8: Tremor: atax[ia]: both legs almost gone'), and post-mortem results ('Typ[ical]. lesions') of cynomolgus monkeys injected with polio virus in Flexner's laboratory. Source: Simon Flexner Papers, American Philosophical Society Library, B/F365, Laboratory Notes, Miscellany #1. Courtesy American Philosophical Society Library.

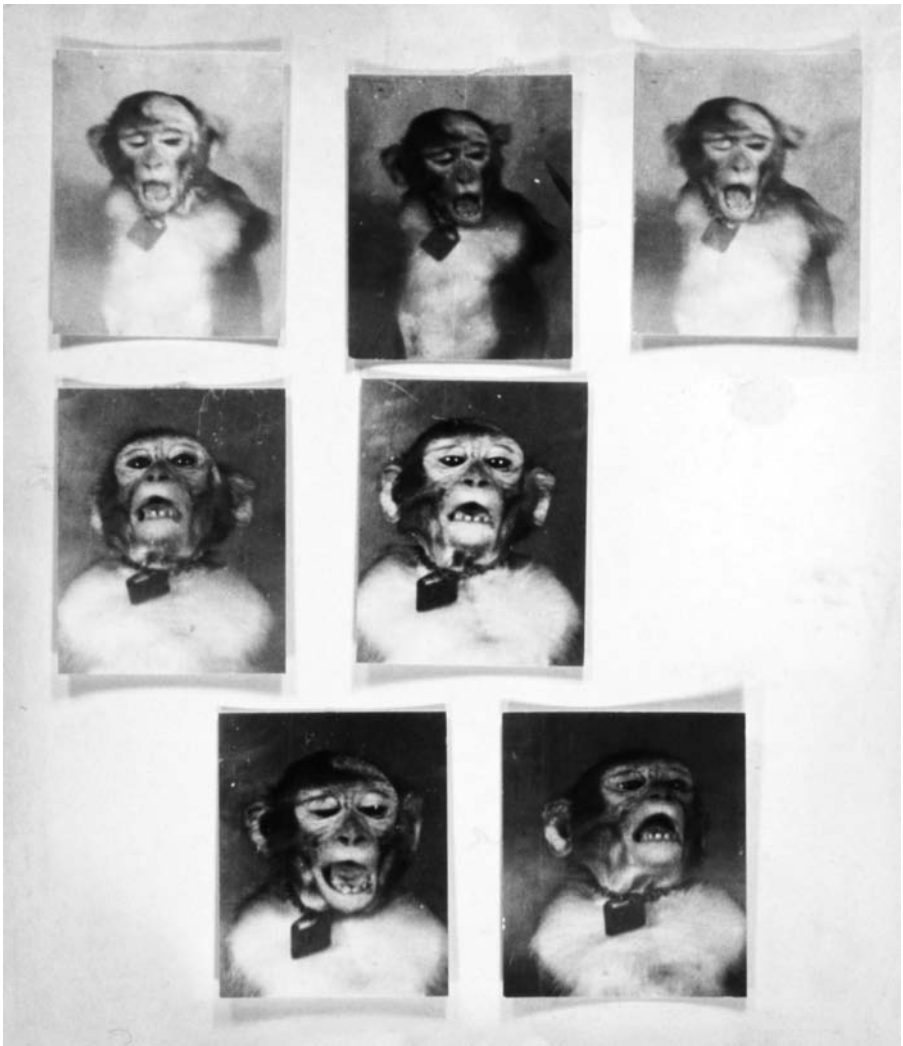

Figure 7.5 Unpublished enlargements taken from a film of a monkey (M.1593) in Flexner's laboratory, probably following an injection of polio virus. Source: Simon Flexner Papers, American Philosophical Society Library, B/F365, Ms. Coll #33, n.d.. Courtesy American Philosophical Society Library.

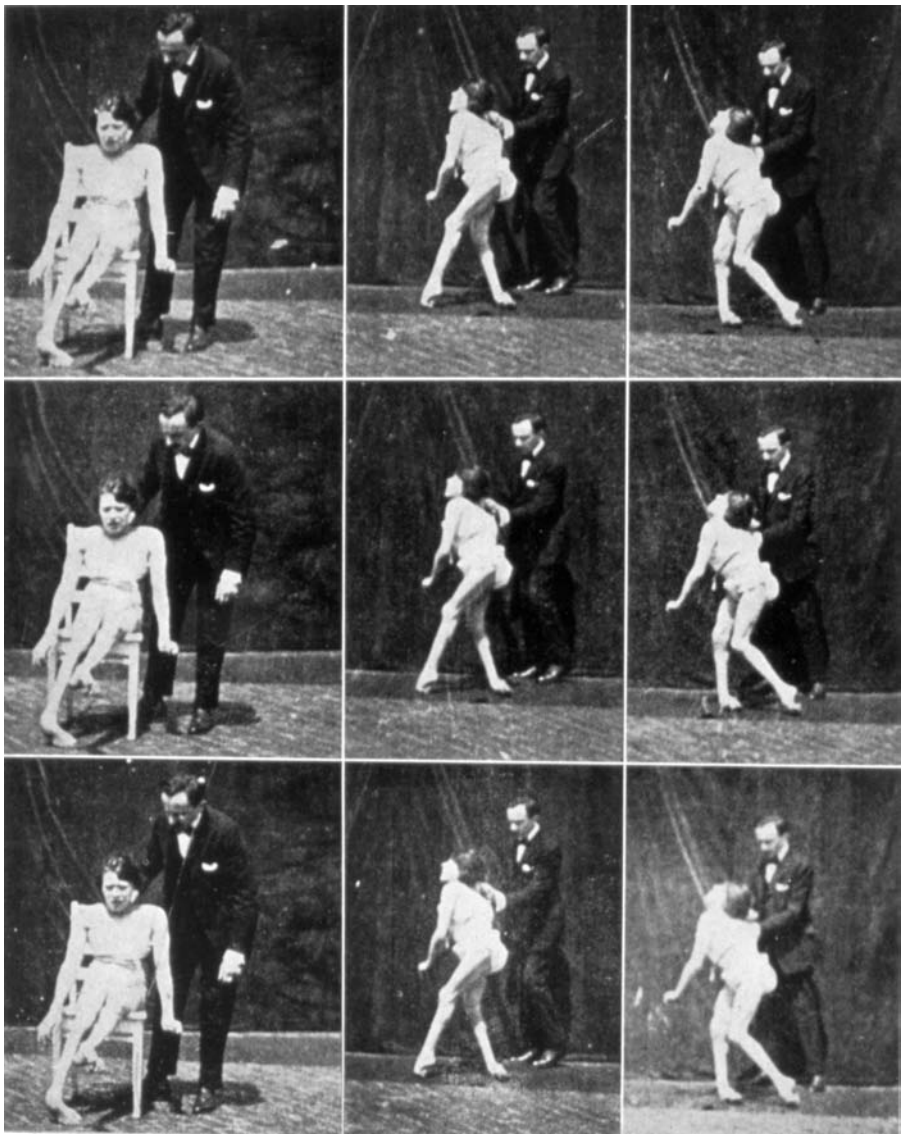

Figure 7.6 Enlargements taken from a film of a patient suffering from 'Dystonia Musculorum Deformans with Dromedary Attitude'. Source: S. Philip Goodhart, 'Bradykinetic Analysis of Somatic Motor Disturbances. Analysis of Motor Disorders by the Aid of Ultra-Rapid Moving Pictures', *Neurological Bulletin*, **3**, 1921, pp. 295–323 at p. 318. Courtesy of the New York Academy of Medicine Library.

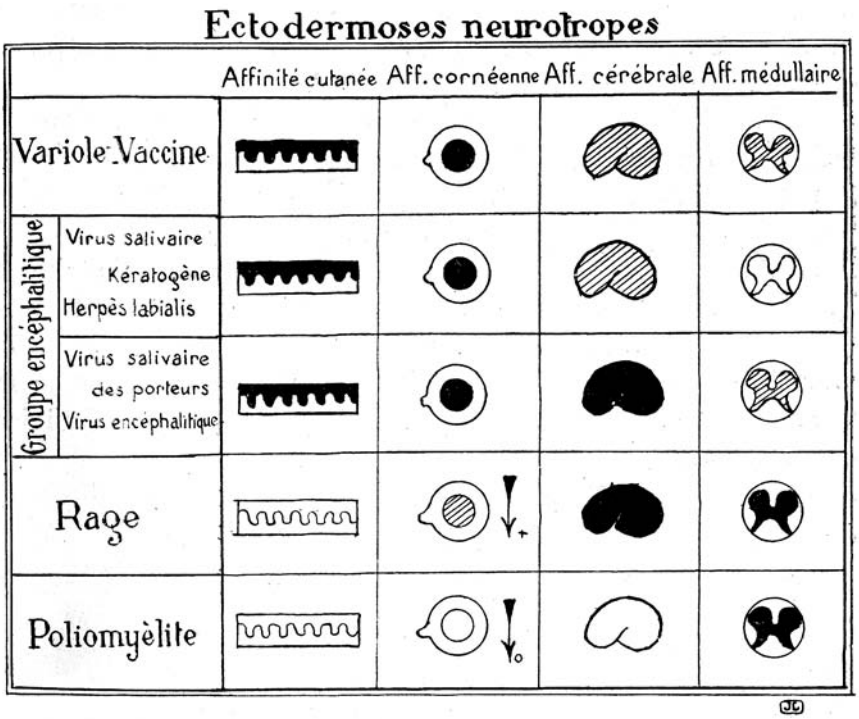

Figure 7.7 Levaditi's table of the neurotropic ectodermatosis group of viruses, illustrating each virus' varying affinity for four different kinds of tissue. The chart is arranged to suggest a continuum ranging from vaccinia, which has a strong affinity (measured in terms of symptomaticity) for cutaneous tissue but only a weak affinity for spinal medulla, to polio virus, which has no affinity for cutaneous tissue but a strong affinity for spinal medulla. Source: C. Levaditi, P. Havier, and S. Nicolau, 'Étude expérimentale de l'encéphalite dite "léthargique"', *Annales. Institut Pasteur*, **36**, 1922, pp. 63–104 and 105–48, at p. 147.

He reached this conclusion just two years after his first publication on encephalitis appeared in 1920, even though he had considerable experience with most of these viruses before. Polio, for example, had been the subject of a number of studies which Levaditi published in conjunction with the Austrian immunologist Karl Landsteiner shortly before the outbreak of the First World War. So why did Levaditi's iconographic system of 'family resemblances' not appear until 1922?

The difference, it seems, was herpes, a strain of which Levaditi received from Robert Doerr, then Director of the Hygenic Institute at Basel, late in 1921.[39] Until 1920, when German and Swiss researchers independently reported their successful transmission of herpetic keratitis (an inflammation of the cornea) through rabbits, herpes had, like encephalitis, been considered to be a symptom of an infectious disease, rather than a disease in itself. Wilhelm Grüter, of Marburg, had successfully transmitted a herpetic keratitis to a rabbit in 1913, but did not publish his results (even as he followed this up by transmitting the infection to the cornea of a blind man). Löwenstein repeated these experiments in 1919, and Doerr demonstrated the existence of a specific local immunity in this procedure in 1920, showing that the infected cornea was refractory to further

infection. Georges Blanc, Director of the Pasteur Institute in Athens, was the first to draw attention to the analogy between some neurological effects of the experimental inoculation of the virus of herpes and the symptoms of epidemic encephalitis. But while the serial transmission of herpetic keratitis assured experimenters that herpes was indeed an infectious disease, encephalitis was another matter entirely. With the exception of Levaditi's work, most reports of successful transmissions of the virus to experimental animals had been discredited by the mid-1920s, most particularly by Flexner. To defend his rather singular success, Levaditi latched on to the fact that experimental herpes could sometimes provoke an encephalitis in rabbits. Following Doerr's lead, Levaditi and his colleagues also claimed to have successfully conducted a number of cross-immunity studies. Animals that survived a corneal herpes inoculation were resistant to corneal or intradural inoculations with encephalitis virus, and animals that survived a keratitis were protected from herpetic inoculations in both the cornea and the brain. There was, it seemed, an immunological identity between the viruses of the two diseases. In this way, Levaditi collapsed the striking clinical differences between herpes and encephalitis, while at the same time revealing a new set of relationships among viruses that could be represented in a powerful visual form.

These relationships resolved around three key concepts – 'virulence', 'affinity', and 'auto-sterilization'. The first was a term Pasteur himself had used in reference to the dynamics of the rabies virus, and it referred to the microbe's varying ability to effect pathological changes in the organism. Taking note of the curious fact that many more individuals showed antibodies to the herpes virus than expressed clinical symptoms, Levaditi demonstrated that the saliva of some asymptomatic individuals could engender a herpetic keratitis in rabbits. This virus could then be 'fixed' in a more virulent form by serial transmission of the virus. Creating (or re-creating) the virus responsible for epidemic encephalitis was, for Levaditi, a mirror image of the process Pasteur had developed to create a vaccine from attenuated strains of rabies. There existed in nature, he argued, weak strains of herpes, the behaviour of which corresponded to that of the 'attenuated' strains of rabies that Pasteur had been able to manufacture in his laboratory.

'Affinity', on the other hand, was a term more frequently associated with the chemical, lock-and-key specificity advocated by Paul Ehrlich. Yet Levaditi invoked it to describe the clinical differences between herpes, which was typically a mild skin disorder, and encephalitis, which could effectively destroy the nervous system. Drawing upon the developmental histology of Ehrlich's rival, Metchnikoff, Levaditi argued that the clinical symptoms masked the underlying similarities between these two infections. The nervous system was, after all, only 'invaginated ectoderm', and skin was merely the external manifestation of this same embryonic ectodermic tissue. Levaditi thus transposed the concept of specificity to a level in between the gross symptoms of patients and experimental animals and the still-invisible domain of side-chain receptors. In his analysis, specificity no longer described a one-to-one correlation between microbe and disease. Nor did it denote the nature of the relationship between antibody and antigen. Rather, it was a way of describing the dynamic affinity of microbe and tissue.

In his description of encephalitis as an 'auto-sterilizable neuro-infection', Levaditi turned once again to Metchnikoff. Metchnikoff had described the immune response as 'phagocytosis', a process in which special cells originating from the mesoderm devoured invading microbes and infected cells. In contrast, Ehrlich's 'side-chain' theory of antibody

formation, which described how cells produced 'receptors' that broke away from the cell and helped neutralize invading 'antigens' by chemically bonding with them, was by 1910 generally accepted as the primary model of immune activity. Many *pasteuriens*, however, continued to describe many immune phenomena, such as sensitization, which encompassed anaphylaxis, allergy and local immunity, in terms of phagocytic activity.[40] Levaditi's description of encephalitis as an 'auto-sterilizable neuro-infection' was part of this institutional tradition that, as Ilana Löwy argues in her contribution to this volume, simultaneously drew from reductionist and holistic precepts. Levaditi argued that the dramatic symptoms of encephalitis were not caused by the direct activity of the virus, but were rather the result of phagocytosis, which disrupted vital nervous activities as phagocytes attempted to devour infected cells in the brain. The severity of this immune response depended upon the organism's sensitivity to what Levaditi now called the 'herpetico-encephalitis virus'. Paradoxically, repeated exposure to feeble doses of the virus seemed to increase sensitivity among Levaditi's experimental animals. Epidemiologically, this cashed out in Levaditi's speculation that encephalitis was the result of neurotropically-virulent but dermotropically-feeble strains of the virus that had entered the nervous system by breeching the mucous membrane barrier in the nasopharynx. The fact that the mucous membranes became inflamed in many infectious diseases explained not only why the some of the symptoms of encephalitis could be found in a wide range of infectious diseases; it also explained why encephalitis had suddenly become rife in the wake of the 1918–20 influenza pandemics. Perhaps more importantly, Levaditi's account had the additional benefit of explaining why the encephalitis virus was so difficult to recover from the brains of encephalitic patients: those individuals had died precisely because their dramatic immune reactions had succeeded in sterilizing their brains of any virus, thus rendering these organs useless in experimental terms. In other words, by the time encephalitis became clinically apparent, the virus had been altogether eliminated.

Levaditi's arguments, and his graphical display of them, were themselves highly visible. In the only section devoted to viruses at the First International Congress of Microbiology, held in Paris in 1930, Levaditi's work and images figured strongly. Indeed, the very name of the session – 'Éléments filterables des Virus neurotropes' – was a tribute to his efforts of the past decade.[41] These efforts had, as I have already pointed out, relied heavily upon icons and diagrams to communicate the true nature of those still-invisible entities that were rapidly becoming part of bacteriological routine. But they also drew upon Levaditi's own pedigree, which was itself rather unique. Before entering Metchnikoff's laboratory in 1900, he had spent a year in Frankfurt working under Ehrlich, who had just become Director of the Royal Institute of Experimental Therapy. Although Levaditi seems to have assigned rather less importance to Ehlich than Metchnikoff or Roux in his intellectual formation, his lifelong interest in the chemotherapy of syphilis bears Ehrlich's imprimatur.[42] So, too, does his passion for creating vibrant diagrammatic lives for his objects of research. But where Ehrlich had adopted the chemical bond as a heuristic for explaining the nature of the antigen-antibody reaction, Levaditi found his histo-pathological expertise perfectly suited for the early study of viral diseases. It was not, after all, solutions, but tissues and cells that provided the only viable media for serial transmission of viruses during the 1920s. While the standardization of such materials has been well described by Michael Bresalier in

his account of British flu studies, within the context of the Pasteur Institute, Levaditi's deployment of developmental concepts and their visual explication by pedigree itself represented a rather different tack on this same problem. His work was a reasonable attempt to adapt Ehrlich's visual strategies to his Parisian institutional context.

Levaditi's work on the frontiers of virus research was nonetheless controversial. Flexner, for one, always maintained that Levaditi had done nothing more than isolate a herpes virus, and that the specific filterable virus responsible for epidemic encephalitis remained to be discovered. As the epidemics disappeared and biomedical interest in the disease dried up by the end of the decade, Levaditi's encephalitis research fell victim to neglect. Its lynchpin broken, his more comprehensive claims about the variability of the neurotropic viruses also disappeared. But the current validity of his work on encephalitis should not distract us from reconceptualizing the role of the visual in the history of early virus research. Turning these 'creatures of reason' into scientific objects could in some instances require more than simply looking more carefully with more sophisticated instruments. It could equally involve turning viruses into creatures of habit, making them the product of a conjunction of a specific set of visual practices, conceptual perspectives, and biological tools. Despite our tendency to think of seeing viruses as an unproblematic activity – not so very unlike spotting a red-winged blackbird in the thicket – Levaditi's icono-temporal schemes suggest an alternative that appealed to at least some investigators during the 1920s. In such a world, seeing a virus amounted to picturing its dynamic relationships with other viruses, as well as with its host, which, in practical terms, could be described as both tissue (the infectious material) and organism (the infected animal). From this perspective, Levaditi's diagrams are more than antiquarian curios; they signify the depth of a kind of reasoning about viruses that could not be reduced to the physio-chemical approaches that ultimately provided virology with the greater part of its imagery and its imagination. But, for all its potency as an ideology, 'holism' does not quite capture the nature of this reasoning, as it obscures the very practical commitments sometimes necessitated by virus research of the 1920s. In this instance, 'holism' appears as little more than a label affixed to the products of practice, which could include seemingly fuzzy conceptions of specificity and even outright transformism.

If the sort of icono-temporal thought expressed by Levaditi's diagrams depicted an acceptable kind of reasoning for virus researchers at this time, historians must begin to account for it systematically (as, for example, Bresalier does in his contribution to this volume). What, for example, was the extent of histology's influence on early virus research? On what basis were 'model viruses' (such as Virus III) or 'model viral diseases' (like epidemic encephalitis or herpes) selected, developed, and deployed? And what were the professional orientations, disciplinary precepts, or clinical commitments of their advocates? Were their aesthetic styles incorporated into their laboratory routines? Were they adopted from their clinical work? The answers to questions like these will, I believe, help historians to more carefully incorporate the sometimes astonishing diversity of investigative styles into virology's past. In the process, we can expect increasingly comprehensive accounts of how and why viruses ultimately came to be pictured in the way in which we now know them to be, in the eye, and in the mind.

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Notes

1 See, for example, the images of bacterial species in Edgar M. Crookshank, *A Textbook of Bacteriology*, London: H.K Lewis, 1896.

2 In contrast, see Patricia Peck Gossel, 'Pasteur, Koch and American bacteriology', *History and Philosophy of the Life Sciences*, **22**, 2000, pp. 81–100, for an examination of American bacteriology's origins in natural history.

3 Joel Howell, *Technology in the Hospital: Transforming Patient Care in the Early Twentieth Century*, Baltimore: Johns Hopkins University Press, 1995, pp. 103–32.

4 Pauline Mazumdar, *Species and Specificity: An Interpretation of the History of Immunology*, Cambridge: Cambridge University Press, 1995, pp. 86–97.

5 Alberto Cambrosio, Daniel Jacobi, and Peter Keating, 'Ehrlich's "Beautiful Pictures" and the Controversial Beginnings of Immunological Imagery', *Isis*, **84**, 1993, pp. 662–99.

6 See Henri Bergson, *Matter and Memory*, trans. by N.M. Paul and W.S. Palmer, Cambridge, Mass.: Zone Books, 1988.

7 See R.C. Grogin, *The Bergsonian Controversy in France, 1900–1914*, Calgary: University of Calgary Press, 1988. For the response of French experimental psychologists to some of Bergson's ideas, see chapter three of Kenton Kroker, *The Sleep of Others and the Transformations of Sleep Research*, Toronto: University of Toronto Press, 2007.

8 Kenton Kroker, 'Immunity and Its Other: The Anaphylactic Selves of Charles Richet', *Studies in History and Philosophy of Biological and Biomedical Sciences*, **30**, 1999, pp. 273–96.

9 Émile Roux, 'Sur les microbes dits "invisibles"', *Bulletin. Institut Pasteur*, **1**, 1903, pp. 7–12 and 49–56.

10 Ibid., p. 7. All translations are my own unless otherwise indicated.

11 Ibid., p. 56.

12 See Angela N.H. Creager, *The Life of a Virus: Tobacco Mosaic Virus as an Experimental Model, 1930–1965*, Chicago: University of Chicago Press, 2002, pp. 17–46.

13 Angela N.H. Creager and Jean-Paul Gaudillière, 'Experimental Arrangements and Technologies of Visualization: Cancer as a Viral Epidemic, 1930–1960', in Jean-Paul Gaudillière and Ilana Löwy (eds), *Heredity and Infection: The History of Disease Transmission*, London and New York: Routledge, 2001, pp. 203–41.

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15 Kroker, 'Epidemic Encephalitis' (n. 14).

16 See Francis Graham Crookshank (ed.), *Influenza: essays by several authors*, London: Heinemann, 1922.

17 I have adapted the terms of 'craft' and 'rationalized production' from John V. Pickstone, *Ways of Knowing: A New History of Science, Technology and Medicine*, Chicago: University of Chicago Press, 2000. For a study of the rationalized production of novelty in immunology and its consequences for medicine, see Peter Keating and Alberto Cambrosio, *Biomedical Platforms: Realigning the Normal and the Pathological in Late-Twentieth Century Medicine*, Cambridge, Mass.: MIT Press, 2003.

18 This dispute is, of course, the subject of Ludwik Fleck's seminal analysis of 'thought styles' in science, as described in his *Genesis and Development of a Scientific Fact*. See also Henk Van Den Belt and Bart Gremmen, 'Specificity in the Era of Koch and Ehrlich: A Generalized Interpretation of Ludwik Fleck's "Serological" Thought Style', *Studies in History and Philosophy of Science*, **21**, 1990, pp. 463–79; and Ilana Löwy, 'Les "faits scientifiques" et leur public: l'histoire de la détection de la syphilis', *Revue de synthèse*, **116**, 1995, pp. 27–54.

19 Francis Graham Crookshank, 'The importance of a theory of signs and a critique of language in the study of medicine', in C.K. Ogden and I.A. Richards (eds), *The Meaning of Meaning: a study of the influence of language upon thought and the science of symbolism*, New York: Harcourt, Brace and Co., 1923, pp. 511–37. See also Christopher Lawrence and George Weisz (eds), *Greater Than the Parts: Holism in Biomedicine, 1920–1950*, New York and Oxford: Oxford University Press, 1998.

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25 Constatin Levaditi and Paul Harvier, 'Étude expérimentale de l'encéphalite dite léthargique', *Annales. Institut Pasteur*, **34**, 1920, pp. 911–72. On Netter, see the necrologies by M.R. Debré in *Bulletin de l'Académie de Médicine* (Paris), 10 March 1936, pp. 419–22; and Édouard Rist, *25 Portraits de Médecins Français, 1900–1950*, Paris: Masson & Cie, 1955, pp. 139–42.

26 On inclusion bodies as a sign of viral disease, see Thomas M. Rivers, 'Some General Aspects of Filterable Viruses', in T.M. Rivers (ed.), *Filterable Viruses*, Baltimore: Williams and Wilkins Co., 1928, pp. 3–52. See also Rivers's indispensable memoir, *Tom Rivers: Reflections on a life in Medicine and Science. An Oral History Memoir prepared by Saul Benison*, Cambridge, Mass. and London: M.I.T. Press, 1967, p. 112.

27 A similar request regarding a different image can be found in item 27.311 from the same archive.

28 C. Levaditi, P. Harvier and S. Nicolau, 'Étude expérimentale de l'encéphalite dite "léthargique"', *Annales. Institut Pasteur*, **36**, 1922, pp. 63–148. I take the term 'virtual witnessing' from Steve

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37 Charles Saunders Peirce, *Collected Papers*, volume 3, Charles Hartshorne and Paul Weiss (eds), Cambridge, Mass.: Belknap Press of Harvard University Press, 1967, §3.361.

38 See Elizabeth F. Cartwright, 'Physiological Modernism: Cinematography as a Medical Research Technology, 1895–1960', Chapter 2, Ph.D. thesis, Yale University, 1991. My thanks to Kady Shear for bringing this reference to my attention. The use of film in the study of epidemic encephalitis will be discussed in a future publication.

39 See the account given in Constantin Levaditi, 'Etiology of Epidemic Encephalitis: Its Relation to Herpes, Epidemic Poliomyelitis and Post-Vaccinal Encephalopathy', *American Medical Association Archives of Neurology and Psychiatry*, **22**, 1929, pp. 767–803, esp. pp. 770–3. On the history of herpes, see François Chast, Claude Chastel, Gertrude B. Elion, Nicolas Postel-Vinay, Gérard Tilles, *Virus Herpès et Pensée Médicale: De l'empirisme au prix Nobel*, Paris: Imothep/Maloine, 1997.

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42 See L[épine], 'C. Levaditi' (n. 24), p. 536.

CHAPTER EIGHT

Immunology in the Clinics: Reductionism, Holism or Both?

Ilana Löwy

Immunology and the Concept of Biological Complexity in the Interwar Era

In his chapter on the history of the Wassermann reaction, Ludwik Fleck criticized the dominant perception of immune reactions as explained in Julius Citron's classical text. For Citron, immunity was the specific reaction of a well-defined, closed unit – the organism – to invading pathogens.[1] There was an unambiguous external cause – attack – and a precise reaction – defense. He depicted the resulting conflict between body and invading pathogen as the essence of disease. Such a view of immunity, Fleck argued, drastically oversimplified host-pathogen interaction:

> … it is very doubtful whether an invasion in the old sense is possible, involving as it does an interference by a completely foreign organism in natural conditions. A completely foreign organism could not find receptors capable of reaction and thus could not generate a biological process. It is therefore better to speak about a complicated revolution within the complex life unit.[2]

In addition, serogenesis and immunogenesis were not merely reactions to pathogenic microorganisms: these were fundamental biological mechanisms, and were therefore the result of reciprocal changes within the complex life unit. For Fleck, interaction between host and parasites should not be conceptualized in terms of 'attack' and 'defense', but should be seen as a biological process, akin to development, ageing, or cyclic fluctuations in life cycles of parasites and bacteria.[3]

Fleck borrowed his notion of the 'complicated revolution within the complex life unit' from the German biologist, Hans Gradmann. Gradmann proposed to replace the concept of the self-contained organism as the base unit of study with the notion of a more permeable 'harmonious life unit', defined as the relevant unit of study in any given biological investigation. It could be as small as a cell, or as large as a forest.[4] Similarly, Fleck's understanding of serogenesis as a constitutional process was, in all probability, derived from the notion of constitutional serology developed by Ludwik and Hanna Hirszfeld. In 1928, Ludwik Hirszfeld, the most famous Polish immunologist of the interwar era, drew on his own and his wife's studies of inheritable blood groups to propose that immunity was a constitutional property of the organism. Normally-occurring antibodies to foreign blood types, he argued, 'should be perceived as biochemical organs, and their genesis and development is submitted to the same laws

as the genesis and development of anatomical organs'.[5] The production of antibodies reflected at the same time the hidden potentialities of the cell, and the consequences of a specific encounter with an antigen.[6] Fleck quoted Hirszfeld's description of allergy as a 'changed mode of reaction' in his book and it is reasonable to assume that Fleck was familiar with other aspects of his work as well.[7] Fleck was persuaded that Gradmann's and Hirszfeld's views represented future trends in biological and medical research. The chemical perception of life, grounded in what Fleck referred to as 'misguided attempts to explain the whole, or nearly the whole of biology in terms of effects produced by chemically defined substances', was, he argued, being replaced gradually by a more complex view of biological and pathological phenomena.

Fleck's and Hirszfeld's views of the complexity of biological processes can be described as holist. On the other hand, these scientists strove to find a concrete and material basis for biological phenomena. Yet, Fleck strongly opposed attempts to explain all biological reactions as simple interactions between well defined chemical substances, or a 'lock and key' view of the chemistry of life. He adhered to an alternative 'molecular vision of life', namely, a colloidal one:

> … the primitive scheme based upon activating and inhibitory substances is being progressively discarded in accordance with current physico-chemical and colloidal theories in other fields. We now speak of states or structures rather than of substances, to express the possibility that a complex chemico- physico-morphological state is responsible for the changed mode of reaction, instead of chemically defined substances or their mixtures being the cause.[8]

The Hirszfelds grounded their constitutional serology in a material perception of heredity. Serogenesis, or serological maturation, Ludwik Hirszfeld explained, was the expression of an 'innate necessity [that] originated in the germinal plasm'. It was defined by the localization of genes on chromosomes, and was subjected to the usual rules of heredity.[9] Hanna Hirszfeld was even more precise. She coined the terms 'chromosomal lesions' and 'genotypic diseases', and prophesized that soon the study of such chromosomal lesions would become as scientific as 'our best studies of morbid syndromes'.[10]

Holist investigations of immune phenomena were often intrinsically bound with attempts to find an appropriate material framework.[11] The intersections between immunology and clinical medicine in France, between 1910 and 1940, illustrate a close inter-relationship between holist and reductionist explanatory frameworks. Immunology played an especially important role in shaping medical practices in France because it was able to provide a bridge between a strong Pasteurian heritage and an equally strong clinical tradition.[12] However, this particularly French fusion of holism and reductionism and its associated clinical practices were abandoned after World War II, and may be viewed today as an example of a poor medical science of a bygone era. This essay proposes a different view. Developments in interwar France point to unresolved issues in immunology, and its forgotten history raises methodological questions on writing the history of this domain.

Anaphylaxis between Specific and Non-specific Reactions

In 1913, the French Academy of Sciences held a poetry competition commemorating the 100th anniversary of the birth of Louis Pasteur. The winner of the competition was Charles Richet, professor of physiology at Paris's Medical School, and a recent laureate of the Nobel Prize in Physiology or Medicine. Richet was also a published novelist, playwright, and essayist. His epic poem, 'Pasteur's Glory' had, in fact, two heroes: Pasteur, and his adversary, the pathogenic microbe.[13] 'Pasteur's Glory' presented the 'Pasteurian Revolution' as a watershed in the history of medicine. However, at the time of its publication, many leading French physicians – including the most enthusiastic supporters of 'Pasteurian Science' – were increasingly shifting their attention from the study of specific diseases induced by pathogenic microorganisms to the investigation of systemic and poorly defined pathological states. The transition from a focus on specific causes and specific cures to a focus on loosely defined pathological states and non-specific therapies was mediated by the concept of anaphylaxis.

Anaphylaxis – a violent reaction to a second injection of a sensitizing substance – was seen as akin to immunity and was initially characterized through its exceptionally high level of specificity. Sensitized animals reacted to a sensitizing substance, and to this substance only: guinea pigs sensitized with horse serum, for example, did not produced anaphylactic shock if injected with serum of a different animal species. A sensitized animal reacted to a minute quantity of the sensitizing substance. This observation led scientists to attempt to apply this exquisitely specific physiological reaction to forensic medicine in order to distinguish between small quantities of organic substances, such as stains made by human and animal blood. Nevertheless, during the 1910s and '20s, French doctors increasingly identified anaphylaxis with a wide range of non-specific and often poorly defined chronic diseases. Their understanding of anaphylaxis led to attempts to develop systemic therapies able to correct a presumed physiological imbalance.

Richet and Paul Portier had first described anaphylaxis in 1902. Portier and Richet noticed that dogs that survived a non-lethal injection of a poisonous protein succumbed very rapidly when they received a second dose of the same substance. Portier and Richet coined the name 'anaphylaxis' – as opposed to 'phylaxis' (protection or prophylaxis) – and noted that the anaphylactic effect was produced only if the second injection was given after a sufficient amount of time had elapsed since the first injection.[14] Richet viewed anaphylaxis as a perfect illustration of the specificity of life chemistry. He conceived of the organism as a collection of chemical mechanisms, and nothing else. This assemblage was, however, constituted by a specific kind of chemical mechanism. Unlike the traditional analytic chemistry developed by the eighteenth-century chemist Antoine Lavoiser, where reactions operated on a scale that could be easily measured and quantified, the chemistry of life was an entirely new kind of chemistry, a 'chemistry of imponderables'. Physiologically significant chemical reactions in living organisms often involved only minute amounts of active substances, but such 'imponderables' could be responsible for very violent and life threatening reactions.[15]

In the early twentieth century, anaphylaxis and allergy – phenomena induced by infinitesimal quantities of chemical substances – were thus simultaneously conceived of as important biological phenomena and as reactions that pointed to the mechanisms underlying numerous pathological events. Moreover, an 'idiosyncratic' intolerance

of foodstuffs or medication was thought to be induced by a minute amount of stray proteins entering the blood stream. Richet argued that this observation indicated that anaphylaxis was not merely an artifact of the laboratory, nor an iatrogenic side effect of serotherapy, but an important physio-pathological phenomenon.[16] Other researchers affirmed that the histo-pathological changes in the lung of a guinea pig suffering from anaphylactic shock, for example, were analogous to pathologies present in individuals suffering from bronchial asthma – another indication that such shock was closely related to human disease. The higher frequency of severe reactions to injections of foreign serum in patients suffering from asthma, urticaria, exema or hay fever further sustained the hypothesis of a continuum between mild allergic phenomena and severe anaphylactic symptoms.[17] In the interwar era, French researchers linked anaphylaxis to a broad spectrum of chronic pathological manifestations. Thus some French physicians argued that therapies should focus on the elimination of functional perturbations and the restoration of a physiological equilibrium and should not be aetiologic, but 'function regulating'. Such a view was energetically promoted by Fernand Widal and his collaborators.

Widal and His Followers: Clinical Models of Anaphylaxis and Their Therapeutic Implications

Fernand Widal, one of the pioneers of medical bacteriology in France, is mainly known for his studies of typhoid fever and of puerperal fever. From 1913 on, Widal became interested in allergic phenomena and argued that they reflected an individual's predisposition for instability in their homeostatic colloidal chemistry or, in his terms, 'colloidal diathesis'. Diathesis was a nineteenth-century medical concept describing a global predisposition to morbidity. It was associated with terms such as 'terrain', 'constitution', 'idiosyncrasy', or 'temperament'. On the other hand, Widal, like Richet, strongly adhered to a chemical vision of life, and to a belief that major medical problems would be solved through a better understanding of the physico-chemical properties of cell components. The concept of 'colloidal diathesis' was an effort to describe a predisposition to a broad array of diseases in chemical terms.[18]

In 1913, Widal and his collaborators studied a sheep merchant who became allergic to wool and developed acute asthma when near sheep. During these crises Widal observed specific changes in the patient's blood which he described as a 'hemoclastic crisis'. Such crises were associated with several clinical signs, including a decrease in arterial pressure, a diminishment of the number of circulating white blood cells, and modifications in the mechanisms of blood coagulation. These changes, akin to those observed during anaphylactic shock, were named by Widal 'colloidoclastic shock'.[19] Coloidoclastic shock, Widal proposed, was a specific case of 'proteinic' or 'peptonic shock'.[20] Injecting a foreign protein into a sensitized subject started a cascade of events which included a massive release of destructive chemical agents into the circulation. These destructive pathways occurred in diverse clinical events such as tissue necrosis after surgery, and were induced by pathogenic agents and diseases which involved spontaneous lysis of cells. These pathways provoked perturbations of the colloidal equilibrium and induced severe pathological manifestations, especially in people with a hereditary predisposition.[21] The treatment of patients suffering from colloidoclastic shock – whatever its initial cause

– aimed to restore the equilibrium of body fluids through a process of desensitization. Thus, Widal and his colleagues treated patients who had experienced colloidoclastic shock with injections of proteins, bacterial antigens, and autologous or heterologous serum. One popular therapy consisted of an intramuscular injection of the patient's own blood or serum; another involved the injection of milk proteins. Widal's favored treatment was the injection of Witte's peptone, a semi-standardized preparation of hydrolyzed protein products which could have been purchased commercially.[22] This was the only preparation Widal used that was commercially available. Other substances, such as milk proteins, or a patient's own serum, were presumably prepared in the hospital ward.[23]

Widal's leading position in the French medical establishment favored the wide diffusion of his ideas. Among his followers was Auguste Lumière, a chemist, industrialist and pioneer of cinema technology. Lumière owned a factory which produced laboratory equipment and reagents. He developed an interest in scientific photography and cinema, and, in parallel, in the chemistry of life and in phenomena of cellular metabolism and regeneration.[24] Lumière's reflections on the chemistry of life were summed up in a series of widely diffused books published in the 1920s and '30s. Lumière took Widal's hypothesis, that the main effect of anaphylaxis was the modification of physico-chemical properties of cells, as a starting point. He extended this definition by claiming that all the reactions of living matter could be explained as changes in the flocculation properties of colloids. A great number of diseases were the consequence of this 'humoral instability'.[25] This was especially true for chronic diseases of anaphylactic origin, such as urticaria, dermatoses, arthritis, rheumatism, migraines, and asthma. These pathologies reflected disturbances of flocculation induced by the putative changes in 'micellae' – the elementary units which structure colloids. Simple chemical substances that could stabilize the colloidal state of the cell and limit the chaotic flocculation were seen as the most effective treatment for these disorders.[26]

Arnault Tzank, a leading French physician (remembered today mainly as a pioneer of blood transfusion) agreed that anaphylaxis was at the origin of many chronic diseases.[27] For Tzank, the ideal treatment for anaphylaxis would desensitize the patient to the specific trigger. Alas, this approach was seldom possible. In many clinical cases of anaphylaxis it was not possible to identify the sensitizing substance to which the patient was reacting. In addition, desensitization sometimes failed to resolve the patient's symptoms or prevent the reaction. When desensitization with the specific trigger was not an option, doctors were instructed to moderate the overall reactivity of the organism through the use of non-specific 'bioactive therapies' such as vaccinotherapy, serotherapy, hemotherapy or proteinotherapy. Serotherapy and vaccinotherapy were seen as specific treatments but, Tzank argued, such a view was inaccurate: their main therapeutic effect was frequently the consequence of a non-specific stimulation of immune mechanisms by bacteria or their products, or by foreign serum.[28]

Alexandre Besredka and Jean Danysz, from the Pasteur Institute, also shared the conviction that many chronic pathologies were induced by anaphylactic mechanisms, and they attempted to develop cures based on the principle of desensitization. Besredka developed a unified theory of sensitivity that claimed that all the immune phenomena – allergy and anaphylaxis, natural and acquired immunity – were different expressions of a single physiological mechanism. The specificity of anaphylactic or immune reactions,

like the 'specificity' of natural immunity, reflected the receptivity of target cells to pathogenic germs or, alternatively, their capacity to react to toxins, rather than being a process dependent on the chemical specificity of humoral antibodies. The main difference between an absence of anaphylactic sensitivity and induced desensitization was the way in which the end-result – the absence of reactive cells – was obtained. Similarly, a naturally immune or non-sensitized animal was devoid of 'reactive cells'. In an artificially immunized or desensitized animal these cells were either depleted or inactivated.[29] This theoretical principle led to the development of Besredka's 'antivirus' therapy. Antivirus – the filtered supernatants of old bacterial cultures – was expected to inactivate reactive cells, and therefore put an end to a chronic anaphylactic state.[30] In the interwar era 'antivirus', usually prepared with a mixture of common pathogenic germs, was produced and marketed by numerous pharmaceutical laboratories. It was used to treat chronic infections such as boils, infected burns, pyodermatitis, carbuncles, sinusitis or acne, and systemic diseases of a suspected bacterial etiology, such as rheumatoid arthritis.[31] Antivirus was the only one among the substances discussed in this text that had a true commercial career. It is hard to know how many patients received antivirus therapy, but the impressive number of laboratories that produced it attests to its popularity. In the inter-war era, antivirus was produced by thirty-three French laboratories and thirty-two foreign ones. It was manufactured by major pharmaceutical firms such as *Behring Werke* or *Institut Mérieux*. In addition, other laboratories sold therapeutic products that were marketed as having been inspired by Besredka's insights.[32]

Danysz proposed a slightly different therapy for chronic diseases using bacterial products. He believed that, over a long period, patients could become sensitized to common bacterial substances through casual contact with foreign proteins from bacteria of the intestinal flora. This was the underlying pathologic mechanism responsible for many idiopathic chronic diseases and 'idiosyncrasies'. Desensitization with an appropriate bacteriological substance would eliminate the source of such chronic anaphylaxis.[33] Accordingly, Danysz developed and marketed – on a very modest scale – a preparation made with an extract of six main intestinal bacilli. He reported that treatment with this preparation led to a marked improvement of gastro-intestinal troubles, skin diseases, rheumatisms, arthritis, and neurasthenia, and it occasionally induced remissions in patients suffering from mental disease.[34]

Pasteur Vallery Radot, Pasteur's grandson and biographer, and one of the leading French clinicians of the interwar era, attempted to bridge the clinical and experimental understanding of allergy and anaphylaxis. He proposed that the generic term 'anaphylaxis' actually covered two types of phenomena. One was the brutal shock observed in laboratory animals following a second injection of foreign protein, or in patients sensitized by a previous injection of therapeutic serum. These reactions were induced by a massive liberation of histaminic compounds to the blood stream. The other less dramatic type of anaphylactic phenomena were the pathophysiological events observed in people suffering from allergies or idiosyncrasies, who were sensitized in a gradual manner. These people presented the signs of complex humoral perturbations described by Widal as colloidoclastic diathesis.

Since physicians did not know how to re-establish humoral equilibrium, allergic and anaphylactic phenomena had to be treated through desensitization. In the majority of cases, the cause of sensitization remained unknown, so the only treatment option was

a non-specific desensitization using a variety of substances such as bacterial products, foreign proteins, auto-hemotherapy, protein shock, or generic preparations such as Witte's peptone.[35] Vallery Radot became an outspoken advocate of using bacteriological products for desensitization. He argued that it was a cutting edge development in physiopathology. The president of the French Medical Association, Fernand Bezançon shared his views. In a presidential address of 1932, Bezançon explained that physicians had left behind the notions of narrow chemical specificity, focusing instead on the broad physio-pathological mechanisms involved in disease, and on specific dynamics of development of pathological phenomena in each patient. They were abandoning attempts to provide specific medications for each disease, replacing this approach with the deployment of drugs which acted on the reactional modalities presented by the patient in various stages of the illness: chemical specificity would be replaced by physiological specificity. Vallery Radot's peptone therapy, Bezançon added, exemplified this trend leading the way for further developments in medicine.[36] For Bezançon, as for Vidal, intervention on 'reactional modalities' of each individual patient was a more precise therapeutic approach than disease-oriented treatments.

Conclusions: Past and Present of the Holism/Reductionism Division

Between 1914 and 1930, French clinicians developed global theories of disease that extended notions of anaphylaxis to a vast range of pathological phenomena, and in a physio-chemical – or colloidal – vision of life.[37] In the 1910s, leading French doctors loudly proclaimed their faithfulness to Pasteur's heritage but were aware of the fact that the bacteriology laboratory seldom provided cures. Anaphylaxis – viewed as a result of the sensitization of tissues and organs to bacteria and foreign proteins – helped to bridge the gap between Pasteurian science and clinical experience. Anaphylactic phenomena were at the same time highly specific, at the level of sensitization, and highly non-specific, at the level of pathological manifestations. It was possible to construct reproducible experimental systems to study anaphylaxis in the laboratory. On the other hand, the wide range of individual differences in reactivity adequately explained the variability of clinical manifestations. Concepts such as 'sensitization', 'chronic anaphylaxis' and 'colloid perturbation' provided a scientific framing for vague and poorly defined symptoms. They legitimated symptomatic therapies and, at the same time, linked Pasteurian sciences with observations at the bedside.

The 'colloidal vision of life', a broad physiological definition of immunological reactions, and a conviction that many diseases had an anaphylactic component, were not uniquely French conceptions. For example, in 1927 the leading US microbiologist Hans Zinsser described immunology as a 'branch of general physiology'.[38] Immunology, he explained, was the study of allergy or the general capacity of the cell to react to stimuli including the production of antibodies and anaphylaxis. Such reactions were responsible for the majority of pathological manifestations in infectious diseases. Inflammation, extensive edema, hemorrhagic transudation, and necrosis were classified as allergic and anaphylactic phenomena that might persist long after the infecting microorganism disappeared from the body, and might thus play an important role in the etiology of chronic diseases. The main difference between Zinsser's views and those advanced by Widal or Vallery Radot was that while Zinsser focused on experimental studies of

bacterial allergy, French researchers immediately attempted to apply their ideas in the clinic.

The anaphylactic episode in French medicine might be presented as a temporary victory of presumably archaic systemic pathophysiological approaches and a sign of the relative backwardness of French medicine in the interwar era. The 'French exception' came to an end after World War II, when French medicine and biomedicine increasingly came under the influence of developments in North America. In the post World War II era, and especially from the late 1950s on, several leading French biologists and medical scientists argued that, thanks to an injection of new, scientific methods, French physicians could finally abandon their muddled, clinic-based theories and revert to the correct – read reductionist – pursuit of specific treatments for well-defined pathological manifestations.[39]

But how helpful is it to frame the 'anaphylactic episode' in French medicine in terms of reductionism versus holism? This episode may illustrate the difficulty in describing specific clinical practices as either holist or reductionist.[40] French doctors employed the term anaphylaxis, originally a description of a highly specific phenomenon, in order to explain non-specific physiopathological manifestations. In the 1910s and '20s, they shifted rapidly between putatively reductionist and putatively holist explanatory frameworks, smoothly substituting one for the other, and applied the new concept to produce simultaneously 'more holism' and 'more reductionism'. Their discourse reflects this complexity and multi-functionality – the same practice could be simultaneously presented as acting on a level of the organism as a whole, and as addressing a precise physiological problem with well targeted means. Conceptually, it may correspond to Charles Rosenberg's 'organismic holism', an idea that turns on understanding the body as a functioning unit and emphasizing the patient's biological particularity.[41] French doctors aspired to address this particularity by modulating specific chemical mechanisms and 'molecularizing idiosyncracy'.

Holism and reductionism tend to be presented either as complementary or as antagonistic. In clinical practice, however, they are often neither. There are no fixed, stable or coherent relationships between approaches focused on the sick organism as a whole and those interested in isolated phenomena, be they on the tissue, the cellular or the molecular level. Doctors who grapple with complicated, multi-layered and slippery pathological phenomena tend to tinker with the conceptual and technical resources at hand, and are more often guided by ad hoc considerations than by a drive for theoretical coherence. Indeterminacy, boundary concepts, and practices are therefore essential elements in medicine. Medicine works as a scientific approach, a socio-cultural system, a profession, and an institution *because* it is heterogenic, and because it provides multiple, and partly incommensurable, interpretative frameworks. The heterogeneity of immunological approaches was, and is, a major asset in the development of this discipline.[42]

The tendency to combine highly precise analyses on the molecular level with loosely defined systemic analyses did not disappear with colloidal diathesis and other mysterious pathological entities fashionable in the first half of the twentieth century. After World War II, the rapid expansion of biomedical research dramatically increased the possibilities to study pathological changes on a molecular level. However, the rapid accumulation of tests and of data did not always facilitate clinical decisions. Doctors

need to separate the normal from the pathological, and they combine information that originates in the laboratory with other ways of apprehending human disease, from the epidemiological to the cultural and the psychological. From the clinician's point of view, sometimes more may be less, and sharper lenses may produce a more confused global image. Present day physicians continue to struggle to align data from the laboratory and the clinics. They occasionally solve this difficulty through the use of rhetorical devices such as polysemic terms, multiple levels of meanings, and imperfect translations. 'Diathesis', a fuzzy term that allowed the combination of pathophysiological, hereditary and chemical explanations, is perhaps not so different from 'asthma', a disease that may be framed as a physiological, a psychological, or an environmental disorder, and may be seen as a concept that favors the production of both more reductionism and more holism.

One message of this paper – the call for historians of science to pay attention not only to professionally and institutionally sanctified developments, but also to domains of study labeled as mundane and unimportant – may be seen today as an attempt to storm open doors. Once the small group of historians of immunology focused mainly on subjects seen as important by immunologists themselves: from the quest to unravel the chemical nature of antibodies and of antigens of the major histocompatibility complex, to the origins of the clonal theory of antibody formation. Historians neglected domains seen as lacking theoretical clarity or too close to practical applications – that is, the great majority of the developments in immunology. This is no more the case. Historians of immunology increasingly follow Fleck's advice to study what the scientists do, not what they say they do. Histories of the major theoretical debates in immunology are an important topic of study, but so are the areas of immunology once seen as marginal: allergy and food allergy, vaccines and serotherapies, skin tests and autoimmunity.

The second message, the need to pay attention to all the different levels of scientific intervention, explanation and justification, is perhaps slightly less obvious. The point is not the promotion of an ideal of a 'definitive study' on a given topic. The decision what to include in order to conduct a complete historical investigation is always a subjective one. Moreover, historians are usually severely constrained by time limits, by their skills, and by the access to sources. One way to overcome some of these constraints is to try to identify the significant 'interpreting details', able to illuminate the whole.[43] Another is an effort to develop a 'fractal approach to the history of immunology' – or striving to capture as much of the large picture as possible, even in the smallest fragments. It may be important to try to keep together several levels of analysis and to pay careful attention to alignments, articulations, and translations, especially to those between the more theoretical and the more practical aspects of immunology. These are surely not the only 'methodologically correct' ways to write the history of immunology – there are many points of view and many methodologically correct approaches – but they may help us to better grasp the complexities of this domain.

Notes

1 Julius Citron, *The Methods of Immunodiagnostic and Immunotherapy*, Leipzig, 1910, quoted in Ludwik Fleck, *Genesis and Development of a Scientific Fact*, Chicago: University of Chicago Press, 1979 [1935], pp. 54–7.

2 Fleck, *Genesis and Development of a Scientific Fact* (n. 1), p. 60.
3 Ibid., p. 61.
4 Hans Gradmann, 'Die harmonische Lebenseinheit vom Standpunkt exakter Naturwissenschaft', *Naturwissenschaften*, 1930, **18**, pp. 641–4 & 662–6.
5 Ludwik Hirszfeld, *Historia jednego zycia*, Warszawa: Pax, 1989, pp. 130–4.
6 Similar ideas were developed by Charles Richet in his speech to the Eighth International Physiological Congress in Vienna, 'Humorisme ancien et humorisme moderne', reproduced in *La Presse Médicale*, 1 October 1910, and published as a separated fascicle by Masson & Cie. in Paris in 1910. The text was also published simultaneously in English as Charles Richet, 'Ancient humorism and modern humorism', *British Medical Journal*, 1910, **2**, pp. 921–6. However, unlike Hirszfeld, Richet did not ground his ideas on the heredity of immunity in experimental data.
7 As far as I know Hirszfeld and Fleck did not collaborate or correspond before the Second World War although they met in a professional context. For example, in 1939, Hirszfeld chaired a session of a meeting of the Polish Association of Physicians and Biologists in which Fleck gave a paper, and he made comments on that paper. See Ilana Löwy, 'Quantification in science and cognition circa 1937: a newly discovered text of Ludwik Fleck', *Science in Context*, 1988, **2**, pp. 345–55. After the war, Fleck became Hirszfeld's protégé. Hirszfeld was the president of Fleck's habilitation jury and promoted his academic career.
8 Fleck, *Genesis and Development of a Scientific Fact* (n. 1), pp. 62–3.
9 Ludwik Hirszfeld, *Les groupes sanguines*, Paris: Masson, 1938 [1928], pp. 125–9.
10 Hanna Hirszfeld, *Role de la constitution dans les maladies infectieuses des enfants*, Paris: Masson, 1939, pp. vi-vii.
11 For example Olga Amsterdamska, 'Stabilizing instability: The controversy over cyclogenic theories of bacterial variation during the interwar period', *Journal of the History of Biology*, 1991, **24**, pp. 191–222; Warwick Anderson, 'Immunities of empire: race, disease and the new tropical medicine', *Bulletin of the History of Medicine*, 1996, **70**, pp. 94–118; Ilana Löwy, 'The immunological construction of the self', in A. Tauber (ed.), *Organism and the Origins of the Self*, Dordrecht: Kluwer, 1991, pp. 43–75; Kenton Kroker, 'Immunity and its other: The anaphylactic selves of Charles Richet', *Studies in History and Philosophy of Biological and Biomedical Sciences*, 1999, **30**, pp. 273–96; Pauline Mazumdar, 'The antigen antibody reaction and the physics and chemistry of life', *Bulletin of the History of Medicine*, 1974, **48**, pp. 1–21; idem, this volume; Barbara Rosenkrantz, 'Immunology as a historical object', *Journal of the History of Biology*, 1994, **27**, pp. 375–94.
12 My argument parallels Ohad Parnes's discussion of the links between immunology and pathology in English speaking countries before World War 1. Ohad Parnes, '"Trouble from within": Allergy, autoimmunity and pathology in the first half of the twentieth century', *Studies in History and Philosophy of Biological and Biomedical Sciences*, 2003, **34**, pp. 425–54.
13 Charles Richet, *La gloire de Pasteur*, Paris: Académie des sciences, 1913.
14 Paul Portier and Charles Richet, 'De l'action anaphylactique de certains venins', *Comptes rendus des séances de la Société de Biologie, Paris,* 1902, **54**, pp. 170–2.
15 Richet, 'Humorisme ancien' (n. 6).
16 Charles Richet, *L'Anaphylaxie*, Paris: Felix Alcan, 1911, pp. 195–8; idem, 'Anaphylaxis', Nobel Lecture, 11 December 1913, in *Nobel Lectures: Physiology or Medicine*, Amsterdam and London: Elsevier Publishing Company, 1967, vol. 1, pp. 473–92, pp. 487–9; idem, 'De l'anaphylaxie alimentaire par la crepitine', *Annales de l'Institut Pasteur*, 1911, **8**, pp. 580–93;

idem, 'Introduction', in Guy Laroche, Charles Richet (fils) and Francois Saint Girons (eds), *L'Anaphylaxie alimentaire*, Paris: J.B. Ballière et fils, 1919, pp. 1–9; Gabriel Richet, 'Les débouts de l'anaphylaxie allimentaire', *Alim'Inter: Le journal de l'allergie alimentaire*, 1999, **4**, pp. 3–8.

17 See, for example, W.H. Manwaring and H.E. Crowe, 'Types of Anaphylactic Reaction', *Proceedings of the Society of Experimental Biology and Medicine*, 1917, **14**, pp. 173–85; J. Auer and P.A. Lewis, 'Acute Anaphylactic Death in Guinea Pigs; its cause and possible prevention', *Journal of the American Medical Association*, 1909, **53**, pp. 459–70; J.A. Kolmer, *Infection, Immunity and Specific Therapy*, second edition, Philadelphia: Saunders, 1917.

18 Fernand Widal, 'Les orientations de la médecine', Leçon inaugurale de la chaire de pathologie interne, 10 March 1911, in Fernand Widal, *Oeuvres Scientifiques*, Paris: Masson, 1932, pp. 727–39. For a general discussion of holism in French medicine in the interwar era, see George Weisz, 'A moment of synthesis: medical holism in France between the wars', in Christopher Lawrence and George Weisz (eds), *Greater Than the Parts: Holism in Biomedicine, 1920–1950*, Oxford: Oxford University Press, 1998, pp. 69–93.

19 Fernand Widal, 'Introduction: Notice sur les travaux scientifiques de M. Widal, à l'occasion de sa candidature à L'Academie des Sciences, Paris, 1918, in Widal, *Oeuvres Scientifiques* (n. 18), pp. 1–7; F. Widal, J. Lermoyez, P. Abrami, E.T. Brissaut and E.D. Joltman, 'Les phenomenes de l'ordre anaphylactique dans l'asthme: La cause hemoclassique initiale', *La Presse Médicale*, 7 January 1914, pp. 525–7.

20 F. Widal, P. Abrami and E. Brissaut, 'Etude sur certains phenomènes de choc observés en clinique: signification de hemoclasse', *La Presse Médicale*, 3 April 1920, pp. 181–6.

21 Researchers had found that a single injection of peptones partly mimicked anaphylactic shock. P. Nolf, 'De l'anaphylaxie', *Archives Internationales de la Physiologie*, **9**, 1910, pp. 407–15; Jean Danysz, *Origine, evolution et traitement des maladies chroniques non-contagieuses: Théorie d'immunité, d'anaphylaxie et d'antianphylaxie*, Paris: J.B.Ballière et fils, 1920, pp. 114–20.

22 F. Widal, P. Abrami and Ed. Brissaud, 'Considerations generales sur la proteinotherapie et traitment par le choc colloidoclastic', *La Presse Médicale*, 5 March 1921, pp. 181–7 ; F. Widal, P. Abrami and J. Lermoyez, 'Anaphylaxie et idosyncrasie', *La Presse Médicale*, 4 March 1922, pp. 189–93.

23 Widal's articles do not provide data about the number of people treated by these different approaches.

24 He was, for example, among the pioneers of studies of cicatrisation. B. Salazard, D. Casanova, J. Zuleta, C. Desouches and G. Magalon, 'Auguste Lumière, pionier de la cicatrisation moderne,' *Annales de la Chirurgie Plastique et Esthetique,* 2003, **48**, pp. 194–9.

25 Auguste Lumière, *Theorie colloidale de la biologie et de la pathologie*, Paris: Etienne Chiron, 1922; idem, *Colloides et mycelloides: Leur role in biologie and médicine*, Paris: Maloine, 1933.

26 Auguste Lumière, *Le problème de l'anaphylaxie*, Paris: Dion, 1924; idem, *Anaphlaxie*, Paris: J.B. Ballière et fils, 1932.

27 Arnault Tzank, *Immunité, intolerance, biophylaxie*, Paris: Masson, 1932, pp. 31–48.

28 Ibid., pp. 150–63.

29 To put it in a nutshell, Besredka argued that, in immunization, if one agrees that the protecting substance is an antibody, protection is an activation of a 'reactive' cell *by* an antibody. In anti-anaphylaxis, if one accepts the view that 'sensibilin' is an antibody, desensitization is an inactivation *of* an antibody which makes the cells 'reactive'. The latter phenomenon can thus be viewed as a return to a normal situation.

30 Alexandre Besredka, *Études sur l'immunité dans des maladies infectieuses*, Paris: Masson, 1928. On Besredka's 'antivirus' see Ilana Löwy, '"The terrain is all": Metchnikoff's heritage at the Pasteur Institute, from Besredka's "antivirus" to Bardach's "orthobiotic serum"', in Lawrence and Weisz (eds), *Greater Than the Parts* (n. 18), pp. 257–82.

31 Alexandre Besredka, *Antivirustherapie et ses applications*, Paris: Masson, 1930.

32 The Besredka file at the Pasteur Institute Archives contains correspondence with antivirus manufacturers, as well as exchanges between Besredka and the Institute directors on this topic. The latter reflect conflicts between Besredka and Institute leaders. The directors of Pasteur Institute refused to launch 'antivirus' production in part because Besredka's ideas were not seen as theoretically sound or as sufficiently proven. The directors were similarly unhappy to see the Institute's name associated with a substance produced by external laboratories.

33 Danysz, *Origine* (n. 21).

34 Danysz's preperations were among the substances listed in a 1934 report that criticized the fragmentation and poor marketing of Pasteur Institute products, and recommended a radical reorganization of the production services. See 'Rapport de la commission Lacroix', *Report of meeting of the Administrative Council of 21 March, 1934*, Pasteur Institute Archive, Administrative Council Papers.

35 Pasteur Vallery Radot, *Hypersensibilités specifiques dans les affections cutanées: anaphylaxie, idiosyncrasie*, Paris: Masson and Cie., 1930.

36 Bezançon, as quoted by Andrew Mendelsohn, 'Medicine and the making of bodily inequality in twentieth century Europe', in I. Löwy and J.P. Gaudillière (eds), *Heredity and Infection: A History of Disease Transmission,* Harwood Academic Press, 2001, pp. 21–79, at p. 35. Bezançon was a friend and collaborator of Vallery Radot, and a former student of Widal.

37 Weisz, 'A moment of synthesis' (n. 18).

38 Hans Zinsser, 'Hypersensitiveness', *The Boston Medical and Surgical Journal*, **196**, 1927, pp. 387–94, at p. 393.

39 Jean Paul Gaudillière, *Inventer la biomédicine: La France, l'Amérique et la production des savoirs du vivant,* Paris: La Découverte, 2002.

40 On this difficulty, see Christopher Lawrence and George Weisz, 'Medical holism: The context', in Lawrence and Weisz (eds), *Greater Than the Parts* (n. 18), pp. 1–22.

41 Charles Rosenberg, 'Holism in twentieth-century medicine', in Lawrence and Weisz (eds), *Greater Than the Parts* (n. 18), pp. 335–55, at pp. 339–40.

42 Ilana Löwy, 'The strength of loose concepts: Boundary concepts, federal experimental strategies and disciplinary growth. The case of immunology', *History of Science*, **30**, 1992, pp. 373–96.

43 Catherine Gallaher and Stephen Greenblatt, 'Introduction', in C. Gallaher and S. Greenblatt, *Practicing New Historicism*, Chicago: The University of Chicago Press, 2000, pp. 1–19.

CHAPTER NINE

Antitoxin and *Anatoxine*: The League of Nations and the Institut Pasteur, 1920–1939

Pauline M.H. Mazumdar

Introduction

The League of Nations was the embodiment of the search for collective security that followed the Allied victory over Germany in 1918. Its Health Organisation was formally subordinate to its political organs, since it reported to the Council. But like the other technical committees, the Economic, Financial and Transit Committees, its members were supposed to be appointed solely on account of their technical expertise. They were supposed to be indifferent to interests of state, though in Germany, no one believed that for a moment. There the League was seen more cynically as an organisation of the victors.

The League's Health Organisation worked through its subcommittees.[1] One of these was the Standardisation Commission, led by Thorwald Madsen of the Statens Seruminstitut of Copenhagen, who was also President of the Health Organisation as a whole. The Commission's main mandate was to examine and standardise the materials and methods of serology, both the therapeutic serums and the serological tests such as the Wassermann test for syphilis. The serologists of the Standardisation Commission were a representative cross-section from an age when serotherapy was medicine's most effective weapon, and every state had its serum institute. But serum therapy had its limitations: not all sera were as successful as the two originals, anti-diphtheria and anti-tetanus. In addition, there were other interests outside of Madsen's international serological group. This paper discusses one such boundary situation.

The idea of the boundary object has quite a long history as historiographic devices go. It was suggested first by Susan Leigh Star and James Griesemer in 1989. They proposed that the organisation of scientific enterprises created a flow of objects and concepts through overlapping networks from different social worlds.[2] The metaphor was developed by Ilana Löwy in 1994, and applied to the interaction between a self-contained community of specialists, in this case the workers of the Institut Pasteur, and the different groups both clinical and industrial that made use of what the workers produced. The boundary objects here, the products of the Institut, formed a link that bridged these different worlds.[3]

In both of these cases, the historians took the boundary object as a means of successful interaction through a point of contact. This paper, however, makes use of the image a little differently: the boundary objects between the two networks discussed here define a sticking point, rather than encouraging an easy flow between the serologists of the League of Nations and the workers of the Institut Pasteur. Our boundary objects are more like the tall stone that represented the ancient Roman god called Terminus, who marked the limit of a property, and was worshipped with blood.[4]

The little world of the serologists

Standardisation reached medicine and hospitals at the turn of the twentieth century. Like the International Bill of Lading for railway freight of 1881, standardised forms began to appear in hospital records, used both to request tests and to report them. The tests themselves tended to become standardised too.[5] The standardisation of therapeutic antisera began with the assay of the antidiphtheria serum, distributed under government seal from Paul Ehrlich's laboratory, first in Berlin, then in Frankfurt in a new Institute for Experimental Therapy, with Ehrlich as Director. Carola Throm has detailed how every aspect of the production of the serum was tightly controlled by official inspectors embedded in the manufacturing firms: the organisms used, the toxin production, the age and strength of the toxin solutions, the serum horses and their veterinary history, the protocols for their immunisation with the toxin, the collection and pooling of serum, the packaging, numbering, labelling and the official records for every batch, as well as the actual assay of the unit value of the antiserum, according to Ehrlich's method.[6]

The serologists were, as Ludwig Fleck put it, a little world.[7] Most of them had learned their techniques in Frankfurt, giving them a common background in theory and practice even though they and their state serum institutes were spread over every continent. Until the War broke out, Ehrlich's standards and his procedures were internationally accepted. But then the connection collapsed: in 1914, Britain took fright at this dependence on an enemy source, and its Medical Research Committee started to press the government to set up its own standardisation laboratory. At the end of the War, the Committee (now the Medical Research Council) organised a Committee on Biological Standards, with a laboratory in the new National Institute for Medical Research in Hampstead near London. Sir Henry Dale, a one-time visitor to Ehrlich's laboratory, was to run it. Standardisation, said the Council, is indispensable for national safety.[8] The Institut Pasteur, however, already had its own standards and its own distribution network reaching out from Paris into the French colonies of Asia and Africa.[9] So did Washington. As independent centres, they did not really need the stimulus of war to break free of Frankfurt.

The first serological Standardisation Conference was held in London in December 1921. The meeting was held under the auspices of the British Ministry of Health, and was attended by representatives of the state: the Ministry of Health, the Medical Research Council, and the War Office.[10] There was no one there from Germany, even though the development and standardisation of sera was such a peculiarly German field: Germany was not yet a member of the League. Secretary-General Drummond favoured Germany's admission, and Germany wished to apply for membership; but under the circumstances, with disagreements about reparations under the Treaty of Versailles, and

a continuing occupation of the Ruhr towns by the Allies, it was not until 1926 that a formal request came from Berlin.[11] Furthermore, Germany was still excluded from all international scientific meetings under a boycott organised by the British and Belgian Royal Societies.[12] By this time, the War had been over for three years, but its lessons were still overwhelmingly present and its needs still fresh. Anne Marie Moulin has said that the experience of the battlefields made cooperation in an international sanitary order a condition of the peace.[13] The planning of the Standardisation Commission is a case in point. In fact, the impulse for the formation of the Commission was most likely the striking success of anti-tetanus serum in controlling tetanus among the war wounded, and the standardisation problems associated with it.[14]

At the first conference, Thorvald Madsen as Chair introduced the Commission and its mandate: it was to work on the standardisation of the anti-tetanus and anti-diphtheria sera, using the pre-War methods of the Frankfurt laboratory, as well as developing new antisera for the treatment of dysentery, meningitis and pneumonia – gas gangrene was to be added later – and on standardising the serological test for syphilis.[15] The projects on this list had heavy military significance: tetanus, dysentery and gas gangrene had been the army's problems, while the navy's were syphilis and meningitis. A new treaty guaranteeing free syphilis treatment for sailors in every port was currently in preparation, underlining the need for the standardisation and reporting of the Wassermann test for syphilis.[16] Subcommittees of serologists from across the globe divided up the work on the various sera: state laboratories in Austria, Belgium, Britain, Denmark, Italy, Japan, Poland and Switzerland agreed to take part, along with the Institut Pasteur in Paris, and two laboratories in the United States. At the centre was at the Danish Statens Seruminstitut, directed by Madsen, and not the Frankfurt institute, directed by Paul Ehrlich, as it had been before the War.

The second meeting of the group took place in Paris in 1922, at the Institut Pasteur and this time, with a German member present. The Health Committee was deemed to be an expert technical committee to which considerations of nationality and membership did not apply.[17] The Institut Pasteur had wanted to have the first conference in Paris so that France could be first to make the *beau geste* of inviting the Germans back into the scientific community; but that was to happen only at the second conference.[18] The German in question, Wilhelm Kolle, was Director of the State Institute for Experimental Therapy in Frankfurt in succession to Paul Ehrlich who had died in 1916. He was nervous and unwilling at first, and afraid he would be snubbed; but in the event, he did go to Paris, and it was not as bad as he had expected.[19] It was essential to have him there: Kolle as Ehrlich's successor symbolised the toxin-antitoxin system and its standardisation, and state responsibility for its accuracy. Without Ehrlich's bioassay, there would have been no international distribution of sera, and no standardisation.

Each of the subcommittees had between five and seven members, with several individuals appearing on more than one. The Institut Pasteur, with its exceptional breadth of expertise, contributed to all of them. Its group included the Director, Albert Calmette, founder of the Institut Pasteur in Saigon, later Director of the Institut in Lille. He joined Emil Roux at the head of the Paris Institut in 1919, and working on the BCG anti-tuberculosis vaccine. He was responsible for international contacts, and so present *ex officio*;[20] L. Cotoni, dealing with anti-pneumococcal serum; Charles-Henri-Alfred Dopter, Professor of Epidemiology at the military medical school, École du Val-

de-Grâce, and later Medical Inspector-General of the French Army, who took on anti-dysentery and anti-meningococcal sera;[21] Louis Martin, director of the Institut's serum farm at Garches, with anti-tetanus and anti-diphtheria sera, and Stefan Mutermilch with the sero-diagnostic test for syphilis. This last, the syphilis subcommittee, had fourteen people on it, and included almost all of the Standardisation Commission.

A Dysentery Antiserum

The dysentery, pneumococcal and meningococcal antisera were new sera: the problem was not so much to standardise them but to invent them. There was no generally accepted body of work to turn to: it was not even agreed whether serum therapy would in fact help in these infections as it so brilliantly did in tetanus and diphtheria.

Dysentery was a typical army disease known to spread by faecal contamination of water. Military hygiene programmes dated back to the 1860s, following the sanitary horrors of the Crimean War. With all their emphasis on water supply, placement of latrines and the careful selection of campsites, and all the sanitary expertise of the Royal Army Medical Corps, the military still had not tamed it.[22] Wartime medical journals, military and civilian, are full of accounts of dysentery in the trenches, on the Somme, at Gallipoli and Salonika.[23] There were reports of epidemics among British prisoners of war, according to a joint memorandum to the War Cabinet by the Admiralty, War Office, Air Ministry, Colonial Office and Prisoners of War Department of 25 September 1918.[24] It had been rife in the troops on the battlefield, especially in the British Expeditionary Force in Mesopotamia, and had resulted in several thousand men being sent back to hospitals in Britain for convalescence. The British Medical Research Council set up a research project to find out whether the dysentery was amoebic or bacillary. The answer was inconclusive: both were often found together.[25] A Medical Advisory Committee for the Prevention of Disease arrived in Gallipoli in 1915, and reported that most cases were amoebic, but later on changed its mind and reported that 90 per cent were bacillary. In 1916, the Committee arrived in Mesopotamia, and reported that as in other war areas, most of the cases were bacillary, and there would have been even more if they had been investigated earlier in the disease, rather than in the base hospitals. Severe, sometimes fatal, bacillary dysentery lasted a relatively short time, an average of 68 days, according to the *History of the Great War,* while the amoebic kind could become chronic.[26] In May 1918, the Director-General of the Army Medical Services appointed a Committee on Dysentery; in 1921, it reported that the disease, when the patient was actually ill, was bacillary, and the amoebae were virtually harmless. The upshot was that the bloody flux, the epidemic dysentery of armies, was agreed to be bacillary dysentery.

The work on the bacteriology of dysentery dated back to the glory days of the 1890s: it forms a history of clinical immunology in miniature. The first description of a bacterial cause was in 1898 in a Japanese epidemic, by Shiga Kiyoshi from the Institute for Infectious Disease in Tokyo.[27] Shiga went on to prepare a successful antiserum, that shortened the duration of the disease by an average of 25 days, and reduced mortality to about one third, though it was not clear whether the serum contained an antitoxin like the anti-tetanus or anti-diphtheria serum, or whether it was simply bactericidal. Shiga was at the institute headed by Kitasato Shibasaburo, and Kitasato, along with Emil von Behring of Berlin, had been one of the originators of the antitoxin concept. It would

have been natural for Shiga to suppose that his bacillus too produced a powerful toxin, which was why the patients felt so desperately ill, and that the antiserum neutralised it, making them feel better very quickly. The bacteria were described again by Wilhelm Kruse in 1900, this time in a German epidemic.[28] He found that there were two types of bacillus, one, the Shiga type, which caused severe disease, and one milder, similar to a form that had been described in 1900 in the Philippines by Simon Flexner of the Rockefeller Institute.[29] Kruse had also found subtypes that he could distinguish by agglutination tests, and labelled them A to H.[30] A third type of organism came from the Danish Statens Seruminstitut. Here Carl Sonne described another bacterium that like Flexner's did not produce toxin, and hence gave a much milder disease.[31]

Rudolf Kraus and Robert Doerr of the Vienna State Serum Institute had prepared a dysentery toxin, raised an antiserum to it in goats first, then in horses, and tried it out in an epidemic in Krakau in the summer of 1904.[32] The workers in Vienna were loyal to the German serological tradition: they modelled their approach on the von Behring-Kitasato toxin-antitoxin system, and assayed their serum exactly as Paul Ehrlich had done with diphtheria antitoxin in the 1890s. The toxin reacted with its antitoxin just as Ehrlich would have predicted, according to the Law of Multiple Proportions, reproducing the stepped neutralisation curve of Ehrlich's diphtheria *Giftspektrum,* and coming very close to the diphtheria model. But they found that a serum that seemed to have a high neutralising titre *in vitro* did not necessarily have a powerful effect *in vivo.* The two effects seemed to be independent of each other, the binding titre often being high soon after the beginning of the course of immunising injections, but the speed of reaction, which they equated with the therapeutic effect, increasing as immunisation proceeded. They called this property 'avidity': it meant that a serum reacted quickly and that it would work well as a laboratory reagent. The detailed explanation of avidity was to fascinate immunologists for the next fifty years.[33] The bacteriology of dysentery and the antitoxin were fairly well established in the German scientific literature, and had found their way into the standard textbooks well before the War.[34] German clinicians were using the serum successfully, and the Vienna State Serum Institute was producing high titre sera from horses immunised with live cultures and with toxin, covering both the free toxin, or exotoxin, and a possible toxic effect of the bacteria themselves, an endotoxin.[35] By 1909, Shiga's antiserum was accepted as an antitoxin in the German literature: so far, it had fitted perfectly into the existing paradigm.

But that was the German literature, and not everyone accepted it. A confusing array of different organisms, different terminologies and different disease pictures made the international literature contradictory and difficult to use, although the disease was so important to states at war. The British War Office's Committee on Dysentery, having no access to Kruse's A to H typing sera during the War, worked out a typing system of its own. There is no mention in its reports of using an antiserum treatment on cases of dysentery, only of attempts at prophylaxis with a partly-neutralised vaccine.[36]

There was also opposition in Paris. Louis Vaillard, Director of the French military medical school at Val-de-Grâce, Medical Inspector-General of the French Army, had been one of the original Institut Pasteur workers to deal with the anti-tetanus serum.[37] He and his colleague and student, Charles-Henri-Alfred Dopter, then Professor of Epidemiology at Val-de-Grâce, had worked together on the problem of dysentery in the army since the turn of the century. They did not believe that the organism produced a

true soluble exotoxin like tetanus and diphtheria; they felt that it damaged the gut cells locally through an endotoxin. By 1903, Dopter had worked up a vaccine that was to be given by mouth.[38]

When the Standardisation Commission met in Paris in 1922, it was to receive the reports of the various subcommittees named the previous year in London. In the case of the Dysentery Subcommittee, the Statens Seruminstitut set the rules by making an antiserum for comparison that was raised by immunising horses with two samples of Shiga's bacillus. One sample was from the Behringwerke company in Marburg and one from Copenhagen, and both were sent round to the members. The toxin was prepared by emulsifying a whole culture of the bacillus, thus diplomatically by-passing the exotoxin-endotoxin problem. The series of 13 injections often made the horses grow sickly and thin, and created abscesses at the injection site.[39] There was no suggestion here of trying to create an injectable vaccine against dysentery: clearly, this terribly toxic 'vaccine' could never be used on human subjects.

The Dysentery Subcommittee consisted of Jean Cantacuzène of Bucharest, Robert Doerr, now of Basel, Charles Dopter of the Val-de-Grâce, working with the Institut Pasteur, Captain Stewart Douglas of the British Medical Research Council, Hida Otoichi from Kitasato's Institute in Tokyo, representing Shiga, Ludwik Hirszfeld from Warsaw, and Lev Alexandrovitch Tarassevitch from Moscow. Wilhelm Kolle of Frankfurt was added to it later on as a representative of all that Paul Ehrlich had stood for. Shiga sent in a report from Tokyo that was so impressive that the Medical Director, Ludwik Rajchman, himself a dysentery worker under the Medical Research Council during the War, suggested publishing it at once.[40] Ludwik Hirszfeld in Warsaw reported that he had made an effort to distinguish exotoxin from endotoxin, and to try to relate these separately to the nervous system effects and effects on the gut. He could not. Toxicity in either sense seemed to depend on the receptivity of the rabbit involved. Nor could he fix the variability of the toxins, though he had heard that the Frankfurt Institute under Wilhelm Kolle had already made up a standard serum and toxin. Frankfurt, it seemed, was ahead of the game.[41] Indeed, Kolle himself had told Madsen that dysentery serum had made so much progress in Frankfurt that official state-sponsored standardisation, along the lines of the anti-diphtheria serum, was about to begin.[42] At a later date, Hirszfeld came to the conclusion that standardisation was impossible without a uniform race of experimental animals, a problem that tied in with his work on constitutional serology, on the individual response to disease. Responsiveness might be linked to Mendelian inheritance.[43] Tarassevitch in Moscow found something similar: the mice that he tried to use in place of rabbits which were too expensive, also showed marked individual reactions.[44]

Robert Doerr, who had been so hopeful about the dysentery toxin-antitoxin system when he was working with Kraus in Vienna in the first decade of the century, now had doubts. His report mirrors the sense of confusion that enveloped dysentery research. There was still not enough clear data about the specific components of the vaccine, or about the specific aetiology of the cases being treated, a real difficulty with armies in the field. As Doerr reported, specificity was the problem. Cases of known aetiology should be treated with known serum:

> The word 'known' in the sense intended here can only be applied to anti-dysentery serum if the whole of its specific relations have been determined … The more accurately and comprehensively these tests are carried out, the more light will be thrown on the whole group of relations connected with the serum treatment of dysentery, and I therefore urge that the Health Committee of the League of Nations should organise an enquiry with this object in view.[45]

There was no report from the British delegate, Captain Douglas. Madsen as Chair visited him in London, only to be snubbed: Douglas said he was too busy with his new tuberculosis vaccine, and had no time or interest left for anything else.[46] Sir Henry Dale, in charge of the British Medical Research Council's new Committee on Biological Standards and its laboratory, after receiving the dried serum standard prepared by Copenhagen, decided simply to anticipate that this would be endorsed by the Standardisation Commission, and to issue it as the British standard, which he claimed he was obliged to do under the recent Therapeutic Substances Act.[47]

At this point, there was no report from Charles Dopter, the dysentery representative for the Institut Pasteur. Dopter and his senior colleague, Louis Vaillard, Director of the Val-de-Grâce, still did not accept the existence of a dysentery exotoxin at all, even in the severe Shiga cases. They thought that they were dealing with an endotoxin contained within the bacterial body, and with an elective affinity for the mucosa of the intestinal wall. These workers stayed close to the Institut Pasteur tradition as worked out by Alexandre Besredka, who began his career in the laboratory of his fellow-Russian, Ilya (Élie) Metchnikoff. Besredka revered Metchnikoff, and adopted Metchnikoff's emphasis on cellular immunity. He suggested that the dysentery organisms had a specific local affinity for the gut, and it was there in the gut that the fixed phagocytes of the reticulo-endothelial layer conferred immunity. Besredka summed up his thinking in 1925:

> Can we not be permitted to speak of the receptor cells of the intestinal wall as having the same functions in the case of dysentery, typhoid and paratyphoid etc., as the receptive cells of the skin in the case of anthrax, and staphylococcal or streptococcal infection? … There are in the different organs of the higher animals, specialised cells that function as local phagocytes. These react only with certain pathogens, unlike the mobile phagocytes or leucocytes, which throw themselves indiscriminately on any foreign body … [48]

In 1909, Dopter had found a way of vaccinating animals by dosing them by mouth with dysentery organisms emulsified in milk. But his favourite method was another of Besredka's: an oral vaccine composed of bacteria emulsified in an anti-dysentery serum.[49] Interestingly, Hida too believed in an oral vaccine. So did Shiga, although he was too polite to say so. To oblige Madsen, he agreed to work on an anti-toxic serum so as to help the Commission to reach an agreement.[50] It was probably Hida who brought along a paper by his colleague Kanai, comparing the oral and subcutaneous methods of vaccination.[51]

The next full-scale meeting of the Standardisation Commission was in Frankfurt in 1928. Kolle, relieved at the unexpectedly friendly and respectful reception he got in Paris, had enthusiastically invited the participants back to Germany. The reports of the subcommittees covered the anti-dysentery serum, anti-tetanus, anti-anthrax and anti-scarlatina sera, standardisation of tuberculin and blood-grouping sera, and a report from

an international conference on rabies.[52] At Kolle's suggestion, gas-gangrene, another war-time problem, was added to the list for future investigation.

The dysentery project had taken off from a serum supplied by Copenhagen. The work had been done by the Medical Research Council, the Institut Pasteur, the Institute of Hygiene at Basel, the National Epidemiological Institute at Warsaw and at Krakau, the Kitasato Institute in Tokyo, the Institute of Experimental Medicine at Bucharest, and the State Institute of Hygiene in Moscow, as well as the State Institute for Experimental Therapy in Frankfurt, Ehrlich's old institute, now under Kolle's direction. The report says that in the present state of knowledge, the 'only possible approach' was to stick to Shiga's bacillus alone, and determine the anti-toxic titre of the serum by the Ehrlich method in guinea pigs as an index of its therapeutic effect, even though as we have seen, not everyone agreed that that was even relevant. There were still disagreements about the nature and the role of the Shiga toxins; there were also several other dysentery organisms that appeared to produce disease but no free toxins. One is rather reminded of the man looking for his car keys under the streetlight, even though that wasn't where he had lost them. The Frankfurt paradigm was very powerful: it provided the 'only possible approach'.

The recommended assay method was that of Ehrlich, based on the lethal dose of toxin for animals of a given weight and its neutralisation by antitoxin. But there was disagreement about whether the toxin-antitoxin neutralisation curve really followed the law of multiple proportions, as Doerr and Kraus had thought before the war in Vienna. Kolle, Ehrlich's successor in Frankfurt, still thought it did, Hirszfeld did not. If different samples of toxin were taken as a basis, the values for the sera came out quite differently, though the sera always had the same relationship to each other. It seemed therefore, that it would be best to work from a standard serum, not, as in Ehrlich's original protocol, from a standard toxin. There was also the problem of variable response by the test animals, noted by Hirszfeld. It was still not clear whether this seemingly antitoxic serum had an antibacterial, as well as an anti-toxic effect, and whether in fact that was really what gave the clinical result.[53] Nonetheless, the Standardisation Commission went ahead with the agreement on the standard.[54] The oral vaccine with its cellular claim did not come into the picture.

The problems with the dysentery serum were not over yet, however. Kolle had agreed in 1928 to set the Frankfurt serum to match exactly the standard serum sent out by Copenhagen. However, by 1931, it appeared that they did not match; either the Frankfurt serum had become much stronger, or the Copenhagen weaker. The Standardisation Commission was worried. This was something serious: Shiga was contacted, and efforts were immediately begun to compare them both with a serum from Japan, which had originated in Copenhagen. A small group of workers including Percival Hartley from London, Richard Prigge and Wilhelm Kolle from Frankfurt and Kaj Jensen from Copenhagen met unofficially in Copenhagen in November 1932 to try to solve the problem.[55] After much experimental effort, they concluded that the International Standard sera had not declined in value over a period of three years; Hartley's report pointed to a weakness in Kolle's technique as the probable cause of the problem.[56]

The Institut Pasteur at the boundary

Unfortunately, Louis Martin from the Institut Pasteur, now an official member of the Dysentery Subcommittee, was not invited to the Copenhagen meeting of November 1932. Worse, the conversation strayed onto other subjects, including vaccination with formol-modified diphtheria toxin or *anatoxine*, and its possible standardisation in Frankfurt by means of the usual large numbers of guinea pigs.[57] We know a lot about this very short and relatively unproductive meeting because of the intense diplomatic efforts needed to try to explain it away and smooth down angry feelings at the Institut Pasteur when the news reached Paris. The care with which Madsen wrote out his explanation and apology is shown by the fact that he drafted it first in his own Danish, and had it translated into French by the official translators. [58]

Gaston Ramon, Director of the Institut Pasteur's experimental farm at Garches, was essentially the Institut's chief immunologist, and a substantial figure.[59] The diphtheria *anatoxine* was his creation, but the Commission had discussed it without any reference to him. Ramon would not accept Madsen's apologies and explanations, and remained insulted:

> I don't want to discuss the question of the terms committee, conference, commission, sub-committee, meetings of the working group etc. I live entirely in my laboratory, and I don't grasp, or not very quickly, the meaning of these diplomatic terms. However, I begin to understand: in London in June 1931, there was a meeting with a number of colleagues and yourself … The standardisation of the *anatoxine* was discussed for two hours, and a programme of study set up … But no mention of this meeting or this discussion ever appeared in the divers documents I possess … [There was also] a meeting of the Commission on Antidiphtheria Vaccine whose composition is listed in the official report C.H. 1056. In this report, there is a minute of that meeting, and a whole programme of experiments that the Institut Pasteur is to participate in, about which we have not even been consulted … Another meeting, perhaps a working group, took place in Copenhagen at the end of 1932 …[60]

The Institut Pasteur was not a state serum institute. It was not a centre of serology like the Statens Seruminstitut, the Vienna State Serum Institute and the Institute for Experimental Therapy in Frankfurt, although as Ilana Löwy has pointed out, much of its income, especially during the First World War, came from its serum sales.[61] Its tendency, however, was to lean towards vaccination rather than serotherapy. Even at Garches, the Institut's serum farm – where the scaling-up of anti-diphtheria serum production from the original rabbit to that industrial-sized organism, the horse, had been managed[62] – even there, the tendency was to prefer cells to serum in theories, and vaccines to antitoxins in practice. Vaccines were more ambiguous than sera, and less easy to standardise: standardisation was not the central interest in Paris that it was in Copenhagen. As the Institut's director Albert Calmette predicted to Ludwik Rajchman in 1924, soon after the first publication of Ramon's work on the diphtheria vaccine,

> It is quite likely that the whole question of serum therapy for diphtheria is about to be turned upside down by the new work of Ramon, done here … Active immunisation against diphtheria has now been made absolutely harmless and practical – and he has

> demonstrated that it is not the strongest toxins that produce the best serums, but just the opposite!
>
> The revolution is on the march. This is not the moment to have some theory crystallised under the aegis of the League of Nations.[63]

Over the course of the 1920s, as Calmette had foretold, the whole question of serum therapy for diphtheria, and for tetanus, *was* turned upside down, as focus shifted from antitoxin production to the creation of vaccines, from therapy to prophylaxis, using the attenuation of the toxin to *anatoxine* to make it safe for human subjects. The Ramon group at the Institut Pasteur developed *anatoxine* vaccines for both diphtheria and tetanus, essentially by-passing both of the two best anti-toxins.[64]

The *anatoxine* quickly became very popular, so popular that it was difficult to keep up with demand. Gaston Ramon helped by sending out instructions and doses of the vaccine.[65] By the later 1920s, a new network based not on sera but on vaccines had built up, centred on the Institut Pasteur. Reports of users outside France were published in the *Annales,* containing information about large-scale trials of the *anatoxine*: 24,510 individuals vaccinated in Belgium, 369,359 across Canada reported by John G. FitzGerald of the Connaught Laboratory in Toronto.[66] By 1932, at a special session of the American Public Health Association meeting in Montreal, the North American public health providers can be seen gearing up to offer vaccination to the populations they serve: FitzGerald, with Ramon's support, reported that the Connaught was preparing and distributing an *anatoxine*, which he called toxoid, using Ehrlich's word for a modified toxin.[67] At the same meeting, William Park and O.R. Povitzky of the New York Department of Health and Walter Harrison of the National Institute of Health in Washington DC, reported routine immunisation of children with the toxoid.[68] As Anne Marie Moulin has said, because of the sweeping success of his *anatoxine,* Ramon gained great prestige: he was to be proposed for a Nobel Prize in 1935 by Jules Bordet, and named President of the Section of Immunology at the International Congress of Bacteriology in New York in 1939.[69] He developed a worldwide personal correspondence based on the distribution of his treated toxins that went far beyond the Institut Pasteur's usual outreach to its *succursales* in the world of France's colonial connections.[70] A map of the Institut Pasteur *dans le monde* shows seventeen Instituts Pasteur; nine associated Institutes are marked, five in Europe, twelve in Africa, six in SE Asia, and three in South America. All but four are in French-speaking areas or colonies.[71] The new outreach with the production and testing of the *anatoxine* went far beyond this traditional Francophone world. The files contain correspondence dating from the late twenties, with advice, reprints and sometimes samples for laboratories and clinicians all over France, as well as in Argentina, Belgium, Britain, Canada, Czechoslovakia, Denmark, Germany, Greece, Hungary, Italy, Iran, Japan, Lebanon, Palestine, Spain, Switzerland, Turkey, USSR, US and Yugoslavia.[72]

It seems a little harsh to call all this practical activity 'artisanal', in Anne Marie Moulin's words, indicative of an inter-war period *moins glorieuse,* a decline in the history of the Institute and in the history of immunology itself. Historians agree, however, that for the Institute, it was certainly a period of declining prosperity: both before, and even more so after the stock market crash of 1929. In Ilana Löwy's words, the Institute's capital eroded, leaving it more and more dependent on sales of sera and vaccines.

Madsen's Commission, in the midst of struggling with Kolle's problems with the dysentery serum, had also, as we saw above, rather tactlessly set up a subcommittee to investigate the *anatoxine,* in an effort to include the new materials in the Commission's scientific ambit. Diplomatically, Madsen hoped to find a way of bridging over the gap between these two sharply demarcated areas, with their undertones of wartime and nationalist tensions between Paris and Frankfurt.[73] He failed: we find Ramon writing dismissively in 1932 in response to Madsen's personal explanations about the Commission's embarrassing attempts to standardise the diphtheria *anatoxine* without Ramon's help:

> As I already did when you were here, I would like to thank you for coming, and also take the opportunity to say once again,
> A. That it is difficult if not impossible to measure the immunising effect of the different samples of diphtheria *anatoxine* by testing it directly on a vaccinated guinea pig, as the Commission suggests …
> B. [That I would like] to underline the value of the intrinsic immunising power as determined by flocculation.
> C. [That we can] prove the concordance of the antigenic power of the *anatoxine* in flocculation units and its immunising power. Numerous comparative tests on human subjects done by my collaborators and myself, and the results we have accumulated … give incontestable proof. Facts established thus rigorously remain facts; tests done on guinea pigs as your own report shows, are completely useless, and prove nothing.[74]

Since an *anatoxine* by definition was not toxic, the classical Frankfurt-style bioassay of the serologists involving a toxic effect on many guinea pigs seemed clumsy and indirect at best, and difficult to relate to its effectiveness as a vaccine, although the National Institute for Medical Research in Hampstead was to remain faithful to Ehrlich's classic *Dosis letalis* method. Percival Hartley, who was later to lead the Standardisation Division at the Hampstead Institute, had published his own method for assay of the diphtheria toxin in 1922, and stayed with it into the thirties. In his account of the history of active immunisation against diphtheria, he tended to play down the originality of Ramon's contibutions.[75] In Paris, however, an *in vitro* flocculation test, based on colloid precipitation of antigen-antibody complexes, had completely replaced the Ehrlich method; the antigen-antibody reaction produced an obvious precipitate in a test tube, with no animals needed. It was quick and simple compared to Ehrlich's complex, expensive bio-assay method, and it appealed to the colloidalist tendency at the Institut Pasteur.[76] Colloid chemistry was attractive: it seemed to offer a new and modern point of view on the chemistry of life, a chemistry more suited to the proteins and their delicate, reversible, charge-based reactions, and to move away from Ehrlich's structural biochemistry with its firm chemical unions, and from the concepts and methods of Frankfurt.[77] As in the case of the serological test for syphilis, the new tendency, especially in Paris, was to turn to colloidal flocculation tests, and even, as Ilana Löwy points out in this volume, to colloidal explanations of disease.[78]

Madsen and his young colleague Sven Schmidt published a parallel series of tests comparing the results *in vitro ad modum Ramon* and *in vivo ad modum Ehrlich*, with a short note in 1929 in French and 1930 a longer paper in German, with obvious diplomatic intent. Comparison of the two methods of testing showed that they mostly agreed with

each other. But Madsen seems to have been less interested in Ramon's *anatoxine* as a vaccine than in using his colloid flocculation as a quick test to monitor the immune response of the serum horses.[79] Madsen was a serologist at heart.

The turn to colloidal flocculation testing, for the *anatoxine* at least, seems to have been pervasive. As Ramon himself wrote to Madsen in 1933:

> You can assure yourself by reading the publications on this question that the flocculation method is being used more and more. It is the basis for the present progress in the production of diphtheria toxins and *anatoxines* world-wide, or almost (in America, in England, in Belgium, in Holland, in Rumania, in Czechoslovakia, in the URSS etc., and even in Denmark …) which goes to show the value of flocculation units. Its widespread use gives it the force of law.[80]

Ramon knew very well that it was being used, even in Denmark: Sven Schmidt at the Statens Serum Institut had been in close touch with him outside the framework of the Standardisation Commission, in fact since the first publications on the new technique, as his long personal letters to Ramon show. Schmidt must have known that his letters would seem like treason, since the most critical of them are handwritten and not typed by the Statens Serum Institut's secretary. But like Ramon, he was angry and insulted. He felt the Standardisation Commission had neglected his expertise; he took Ramon's side in the argument about the standardisation of the *anatoxine* by the Ehrlich method, and the contentious meeting of 1932:

> Let me begin with some personal remarks about international standardisation. I absolutely agree with you about the make-up of the 'commissions', 'sub-commissions' and 'meetings' etc. … The resolutions passed at the conclusion of those 'conferences' look pretty peculiar to real specialists in the field who have not taken part in the 'meetings'. I remember that you told me when I last visited you in Paris that there had been a meeting when they talked about the Schick reaction, but I was not invited even to that one. I didn't say anything, even though I have done more work on this than most of the members of these various commissions set up by the Standardisation Committee (preparation and issuing of the serums and toxins, standardisation and control of the serums and toxins on demand…) but I never got a single invitation from the Hygiene Committee …
>
> In short, these commissions should have been made up of those who were actually working on current problems instead of people who hadn't touched a pipette or worn a lab coat for the last ten or twenty years. Then we might have hoped to get some usable results … I can assure you that if the President had not been at the same time my boss, I would have given up this project: it takes up a lot of time, and mostly leads to nothing but disappointment …
>
> But to go back to the question of the *anatoxine*. From the beginning, I suggested to the President that we should have a meeting that would bring together all those who have already done experimental work on the *anatoxine* and the flocculation reaction: you, Glenny, H. Schmidt from Marburg and myself. In my opinion, we should have begun with a study and a discussion of the results that have already been obtained by these workers, since there had been some solid experimental work done. Instead, they started off as if there was nothing, and with a plan that was all wrong.[81]

J.G. Fitzgerald of Toronto, who was invited to join the Standardisation Commission in 1933, was keen at once to do comparative testing. As we saw above, he was already

doing very large clinical trials of vaccination with *anatoxine* or 'toxoid' as he called it, sent to him by Ramon.[82] In 1935, the Health Organisation finally issued a study of the two methods by the Statens Serum Institut, which concluded that the 'toxoid' could be standardised by an antigen-antibody flocculation test except in the rare cases when the antiserum chosen was one of unusually high avidity. Copenhagen undertook to circulate a suitable serum for the test.[83]

The Institut Pasteur did cooperate with the Standardisation Commission, but it was a prickly relationship. From 1924 onwards, following the introduction of the *anatoxine*, vaccines became increasingly successful, and the *pasteuriens* became less and less interested in standardisation in general, and the classical Ehrlich assay in particular. The *anatoxine* and the flocculation test on the one hand, and very marginally successful anti-dysentery serum on the other, defined the limits of the therapeutic antisera and the Ehrlich assay method that went with them.

Conclusion

The purpose of the League of Nations was to work toward world peace, through what a contemporary commentator called in 1936, 'collective security based on cooperative universality'.[84] Standardisation clearly fitted into that picture: in 1937, the Health Committee was able to say that standardisation had always received support from the League's Council as a fine example of international cooperation. Nineteen countries in Europe and eleven more in Asia and America had adopted the serological standards they sent out.[85]

The Health Committee's effort to standardise its sera in the interests of world peace and collective security worked out very well in many cases. The diphtheria antitoxin and its twin, the tetanus antitoxin, were enormously successful in clinical practice and fitted the existing technology perfectly: Ehrlich's standardising procedure had been designed to deal with them. The serologists all knew and understood each other, and they knew and understood the Ehrlich protocol: it was their bread and butter. As Fleck had said so tellingly, they were a little world. Sadly, the new dysentery serum did not work out as well as diphtheria and tetanus. There were too many organisms: the Subcommittee concentrated on the Shiga bacillus which did produce toxins; but there were several other dysentery organisms, most of which did not act through a classic circulating toxin and so counted themselves out of specific treatment with antitoxin from the beginning. Like the other bacterial infections for which the Commission had hoped to develop new antisera, that is, streptococcal, staphylococcal and meningococcal infections, the control of dysentery had to await a non-specific therapy, the sulpha drugs, to be introduced only a few months later, beginning in the mid-thirties. The same story has been told about the anti-pneumococcal sera: efforts to treat pneumonia serologically were confused by the many serological subtypes of the organism. Here, too, specific treatment was superseded by the non-specific sulpha-drugs, which swept away everything in their path. The first successful use of sulphanilamide was for streptococcal infections, such as sore throats which often had serious sequelae, and staphylococcal infections such as erysipelas; sulphapyridine came in for meningitis and pneumonia in 1938, and sulphathiazole for dysentery from about 1939. According to Underberg, experiments on the effectiveness of sulphanilamide were also carried out in the concentration camps. The step from the

patented Prontosil to the simpler and more effective sulphanilamide was made by the Tréfouëls, working at the Institut Pasteur. [86]

The network of serologists tied together under Thorvald Madsen in the Standardisation Commission and its subcommittees was a working community that characterises a whole era, an age of serology. The state serum institutes and the serologists, the members of the Commission and its special subcommittees were related by their common ancestry in Paul Ehrlich's standardisation of the toxin-antitoxin system, and its striking successes in the treatment of diphtheria and tetanus. But attempts to extrapolate from that model were less successful; with the new sera, among them the anti-dysentery serum, the method reached a boundary. Even though it had the highest of military priorities, and an anti-Shiga antiserum was in fact standardised and issued, it was not much used in practice. Perhaps that was because it was too difficult to identify specific dysentery organisms under field conditions, or perhaps because it was not clear after all whether the Shiga bacillus really belonged to the exotoxin-antitoxin system. Several workers, including the group at the Institut Pasteur, preferred an oral vaccine to the anti-serum. Interestingly, it has been oral vaccines that have led the way most recently for gut-related infections. In the end, the new sera were overtaken by another German innovation, the sulpha drugs, which appeared in 1935.

It was even more artificial to try to standardise an *anatoxine*, by definition not toxic, by the Ehrlich *Dosis letalis* method, depending as it did upon lethal toxicity in guinea pigs. That was, more or less, the view of the Institut Pasteur, which preferred its own colloidal flocculation tests to the classic bioassay. We see here the formation of another network, a less formal one than the Health Organisation with its committees and subcommittees. It was based not on sera but on vaccines, and centred on the Institut Pasteur. In spite of the income they brought in, the Institut Pasteur was less attached to sera, less interested in standardisation, and even before World War I, a lot more interested in cells and vaccines. The differences were quite clear to the workers involved: we find Calmette as early as 1924, a few weeks after the publication of the *anatoxine* and the flocculation test that went with it, telling off the Standardisation Commission for 'crystallising an old methodology under the auspices of the League'. In spite of Madsen's efforts, both scientific and diplomatic, a successful collaboration between the two networks, the serologists of the Standardisation Commission and the Institut Pasteur and its contacts did not really come about. The Institut Pasteur and its international network of correspondents shifted the ground from serotherapy to vaccination.

Here are our two boundary objects, the rather doubtful dysentery antitoxin on the one hand and the very successful *anatoxine* on the other. They mark a limit and a transition, a limit to serotherapy and its classic bioassays, and a transition to vaccine prophylaxis and the flocculation test. These were the boundary stones that separated the Standardisation Commission from the Institut Pasteur.

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Head of the International Laboratory of Biological Standards, Statens Serum Institut, Copenhagen. The Social Sciences and Humanities Research Council of Canada supported the project under Grant #41092-0305.

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75 (Sir) Percival Hartley, 'The routine preparation of diphtheria toxin', *Journal of Pathology and Bacteriology*, **25**, 1922, pp. 458–67; idem, 'State control of diphtheria prophylactic in Great Britain', in Wilhelm Kolle (ed.), *Wissenschaftliche Woche zu Frankfurt a. M. 2–9 September 1934*, vol. 3. *Probleme der Bakteriologie, Immunitätslehre und experimentelle Therapie*, Leipzig: Thieme, 1934, pp. 81–9; idem, 'Materials used in Great Britain for the active immunisation of man against diphtheria', *Journal of Pharmacy and Pharmacology*, **1**, 1949, pp. 425–35.

76 Gaston Ramon, 'La floculation dans les mélanges de toxine et de serum antidiphtérique', *Annales de l'Institut Pasteur*, **37**, 1923, pp. 1001–11; Ramon, 'L'anatoxine diphtérique: ses propriétés – ses applications', *Annales de l'Institut Pasteur*, **42**, 1928, pp. 960–1009.

77 Pauline M.H. Mazumdar, 'The antigen-antibody reaction and the physics and chemistry of life', *Bulletin of the History of Medicine*, **48**, 1974, pp. 1–21; Wolfgang Pauli, *Physical Chemistry in the Service of Medicine: Seven Addresses*, London: Wiley, 1907, pp. 137–201.

78 Mazumdar, '"In the silence of the laboratory"' (n. 15), pp. 446–55; see also Ilana Löwy, 'Immunology in the clinics: reductionism, holism or both?', in this volume; Löwy discusses Fernand Widal, another *pasteurien*, who proposed a colloidal explanation for anaphylaxis.

79 Thorvald Madsen and Sven Schmidt, 'Flocculation entre la toxine et l'antitoxine diphthériques et standardisation de l'anatoxine', *Comptes Rendus de la Société de Biologie*, **102**, 1929, pp. 882–4; idem, 'Reaktionsgeschwindigkeit zwischen Diphtherie-toxin und Antitoxin und ihre

Bedeutung für die Heilkraft des Antidiphtherischenserums', *Zeitschrift für Immunitätsforschung*, **65**, 1930, pp. 357–84.

80 Ramon to Madsen, ltr d. Garches, 15 June 1933. Archives Institut Pasteur. Fonds Ramon, RAM 5.

81 Sven Schmidt to Gaston Ramon, handwritten ms ltr 'Lettre confidentielle et personnelle', d. Copenhagen, 11 August 1933; Schmidt to Ramon, ltr d. 15 May 1928; 5 January 1929; 15 March 1931; handwritten ms ltr 'Confidentielle', 13 September 1932; handwritten ms ltr 'Confidentiel', August 1933?. Archives Institut Pasteur. Fonds Ramon, RAM 5.

82 James G. FitzGerald to Madsen, ltr d. 2 March 1933. SSI. Th. Madsens Papirer. 1933 II. File: Folkforbundscorrespondance 1933.

83 Société des Nations. Organisation d'Hygiène. Mémoire relatif à un serum-étalon antidiphthérique international destine au titrage par la flocculation, par le Département des Standards Biologiques du Statens Serum Institut, Copenhague (1935) C.H. / C.P.S.B. / 29 (French version only available).

84 George Schwarzenberger, *The League of Nations and World Order: A Treatise on the Principle Universality in the Theory and Practice of the League of Nations*, London: Constable, 1936, pp. 149–51.

85 League of Nations. Health Organisation. *Report to the Council on the Work of the Twenty-fourth Session of the Health Committee,* Geneva: February 5–9, 1937, pp. 18–22. C.148.M.96.1937.III.

86 Michael Worboys, 'Treatments for pneumonia in Britain 1910–1940', in Ilana Löwy (ed.), *Medicine and Change: Historical and Sociological Studies of Medical Innovation / L'innovation en medicine: Études historiques et sociologiques*, Paris: Éditions INSERM, 1993, pp. 317–35; see also Iago Galdston, *Behind the Sulfa Drugs: A Short History of Chemotherapy,* New York, NY: Appleton, 1943, pp. 128–56; Hans-Peter Unterberg, *Die Anfänge der Sulphonamidetherapie in den dreissiger Jahren,* Herzogenrath: Murken-Altrogge 1986, pp. 218, 183–8. Prontosil, the first sulphonamide, was introduced in 1935 by Gerhardt Domagk of I.G. Farben (*Deutsche med. Wochenschrift*, 15 February 1935); it was taken up quickly in England (Leonard Colebrook and Maeve Kenny, *Lancet*, 6 June 1936) and in the US (Perrin H. Long and Eleanor Bliss, *Journal of the American Medical Association*, 2 Jan 1937).

PART IV
Insiders, Immunity and Identity after World War II

CHAPTER TEN

Molecular Surveillance: A History of Radioimmunoassays

Angela N.H. Creager

The development of immunology throughout the twentieth century has had a profound technological edge, as scientists have put the remarkable specificity of antibodies to use in identifying and isolating cells and molecules. This essay focuses on an immunology-derived detection technique that has been widely used in research and diagnostics – that of radioimmunoassays.[1] Radioimmunoassays were the first of a generation of *in vitro* antibody-based assays, including ELISA and fluorescent immunoassays, that enabled users to measure minute concentrations of specific molecules, as small as 10^{-10} to 10^{-12} molar, even in the presence of billion-fold higher concentrations of other molecules.[2] This sensitivity greatly improved upon the immunoprecipitation detection techniques of the mid-twentieth century.[3] Radioimmunoassays generally involve mixing known quantities of a radioactively marked antigen with the antibody to that antigen, then adding an unknown amount of unlabeled antigen, which competes with the radio-labeled antigen for binding sites on the antibody. By measuring how much labeled ('hot') antigen has been displaced by the 'cold' antigen, one can determine the precise amount of the unlabeled antigen present. The sensitivity and simplicity of the method led to its wide adoption in laboratory research and in medical diagnostics.

Like many other techniques for identifying and tracking molecular agents, radioimmunoassays rely on radioisotopes – unstable variants of chemical elements that give off detectable radiation as they decay – to label molecules of interest. The widespread availability of radioisotopes after World War II was facilitated by the US Atomic Energy Commission (AEC), which managed the massive infrastructure of the American bomb project. The Atomic Energy Act of 1946 charged the AEC with pursuing and promoting the civilian benefits of the atomic age. Among the 'medical dividends' of the atom were radioactive isotopes mass-produced in the government's nuclear reactors.[4] The AEC made these radioisotopes available to scientists and physicians and encouraged their use through a combination of training programmes, subsidies, and incentives to companies to produce laboratory equipment and reagents. As part of this enterprise, the AEC began supplying radioisotopes for clinical research and therapy to Veterans Administration (VA) Hospitals. One of the first such units was established at the VA Hospital in the Bronx, New York, where Rosalyn Yalow, a nuclear physicist, and Solomon Berson, an MD, developed the radioimmunoassay technique. Hence the emergence and early history of radioimmunoassay manifest the priorities and resources of the atomic age.

In addition, both the initial development of the radioimmunoassay method and its subsequent application point to the thick connections between the clinic and the

laboratory, a theme that recurs throughout this volume. What is surprising about this case is the dynamic of the scientific transfer: the technique emerged out of clinical research, and then moved into biological research as well as into medical diagnostics. Yalow and Berson were using radioisotopes to trace the fate of insulin in diabetics and other patients that received exogenous insulin. Their 1956 finding of anti-insulin antibodies in patients receiving insulin therapy contradicted the then-dominant dogma that peptides as small as insulin could not stimulate genuine antibody production. The methodology underlying the radioimmunoassay emerged from Yalow and Berson's efforts to demonstrate, in response to skeptics, that the plasma globulin binding insulin in this group of patients was actually an antibody.

The dissemination of the technique can be viewed as a two-step process, as the method first penetrated Yalow and Berson's research field and then entered the realm of commercial diagnostics. In the early 1960s, Yalow and Berson extended their method to develop assays for several other small hormones, including growth hormone, adrenocorticotrophic hormone (ACTH), and gastrin. Other hormone researchers were the first to adopt their technique. By the 1970s radioimmunoassay formed the basis of a new generation of diagnostics in clinical medicine, bringing the method to a much wider base of users. According to one survey, by 1976, 4,108 hospital and non-hospital clinical laboratories in the US performed radioimmunoassays of all kinds.[5] Molecular biologists also adopted the technique in research, in conjunction with related methods such as ELISA and Western blotting.[6] Yalow and Berson never patented their original method, but scientific credit continued to accrue to them as applications for their technique proliferated. In 1977, the same year Yalow won the Nobel Prize (Berson died five years earlier), the Science Citation Index christened Yalow and Berson's 1960s paper a 'citation classic' for having been cited 1,100 times between 1961 and 1975.[7] Radioimmunoassay remains an important tool in medical diagnostics, and also has a place in toxicology, environmental monitoring, and workplace drug testing.

From Atomic Medicine to Radioimmunoassay

The widespread application of radioisotopes in biomedical research became one of the major consequences of the 'physicists' war' for postwar life science.[8] Several historians of biology have stressed the role of physicists in general, and those associated with the Manhattan Project in particular, in the transformation of postwar biology. Evelyn Fox Keller points to the symbolic continuities between a physics tainted by its secretive pursuit of a massive instrument of destruction and the physics-inspired pursuit of the secret of life by molecular biologists. In her view, molecular biology benefited from the high cultural authority of physics while providing it some vindication.[9] Moving the theme of redemptive biology to a more disciplinary level, Nicolas Rasmussen argues that the infusion of funds and people into biophysics after the war – as American politicians and scientists attempted to find a 'silver lining' in the mushroom cloud – seeded the subsequent emergence of molecular biology.[10] My contribution stresses a much more tangible legacy of the war – the redeployment of facilities built for the bomb project to provide postwar scientists and physicians with nuclear-generated radioisotopes. Physical scientists within the Manhattan Project developed and launched this plan,

which was part of their efforts advancing the civilian control of atomic energy after demobilization.[11]

Prior to the war, cyclotrons, exemplified by the massive machines at Ernest Lawrence's Berkeley lab, were the principle source of artificial radioisotopes. Physicists began to collaborate with physicians and biologists in the late 1930s in using these new radioactive sources in research, therapy, and diagnosis. Indeed, the medical uses of radioactive sources – especially in treating cancer – provided an important justification for cyclotron-building in the late 1930s and 1940s.[12] Even so, cyclotrons produced tiny amounts of isotopes at high cost, and access relied on direct interaction with physicists and chemists. For example, in 1937 Lawrence was supplying only a half a dozen biologists with radiolabels.[13]

The development of nuclear reactors, first called 'graphite piles', as part of the Manhattan Project, made available an alternative means for producing artificial radioisotopes. In the course of converting uranium into plutonium for bomb production, the American military's reactors at Oak Ridge and Hanford generated radioisotopes as

Figure 10.1 Unloading of an irradiated sample from the Oak Ridge reactor. Original caption reads: 'Removal of radioactivated sample from the pile after a neutron bombardment. Here Dr Ralph Overman, with a long holder, removed a bombarded sample from the carrier block which has been pulled from the pile. Mrs Weber measures the sample's radioactive strength to check on the safety of handling it. The carrier block is pulled into a lead shield to protect the workers from the radiation of the other samples in the carrier'. X-10, Clinton Laboratories, 14 June 1946. Source: US Army Photograph. Courtesy National Archives, photograph no. 433-OR-box 22-MED-308.

fission products, although in impure form. Iodine-131, whose use in the diagnosis and treatment of thyroid disorders had already been shown, was one such by-product.[14] In addition, foreign 'target' materials could be placed in the reactor to produce specific radioisotopes from neutron bombardment (see Figure 10.1). Several of the isotopes of biological interest, such as carbon-14, sulphur-35, and phosphorus-32, could be produced easily and cheaply this way.

Even before the conclusion of World War II, the head of the Manhattan Project, General Leslie Groves, approved a plan to dedicate the Oak Ridge reactor to mass-production of radioisotopes for outside users (Figures 10.2 and 10.3). Scientists and physicians could utilize radioisotopes in two ways: as *radiation sources*, principally in cancer therapy, and as *tracers* for tagging a molecule of interest with radioactive atoms to follow its movement through tissues or chemical transformations.[15] The headquarters of the Manhattan Project signaled both of these avenues of use in its announcement of the radioisotope program in June of 1946: 'Production of tracer and therapeutic radioisotopes has been heralded as one of the great peacetime contributions of the uranium chain-reacting pile. This use of the pile will unquestionably be rich in scientific, medical, and technological applications'.[16]

Figure 10.2 Aerial photograph of building housing the graphite reactor and process area, Clinton Engineer Works, Oak Ridge. Source: US Army Corps of Engineers, Manhattan Engineering District, 10 March 1944. Courtesy National Archives, photograph no. 433-OR-box 22-roll 206-28.

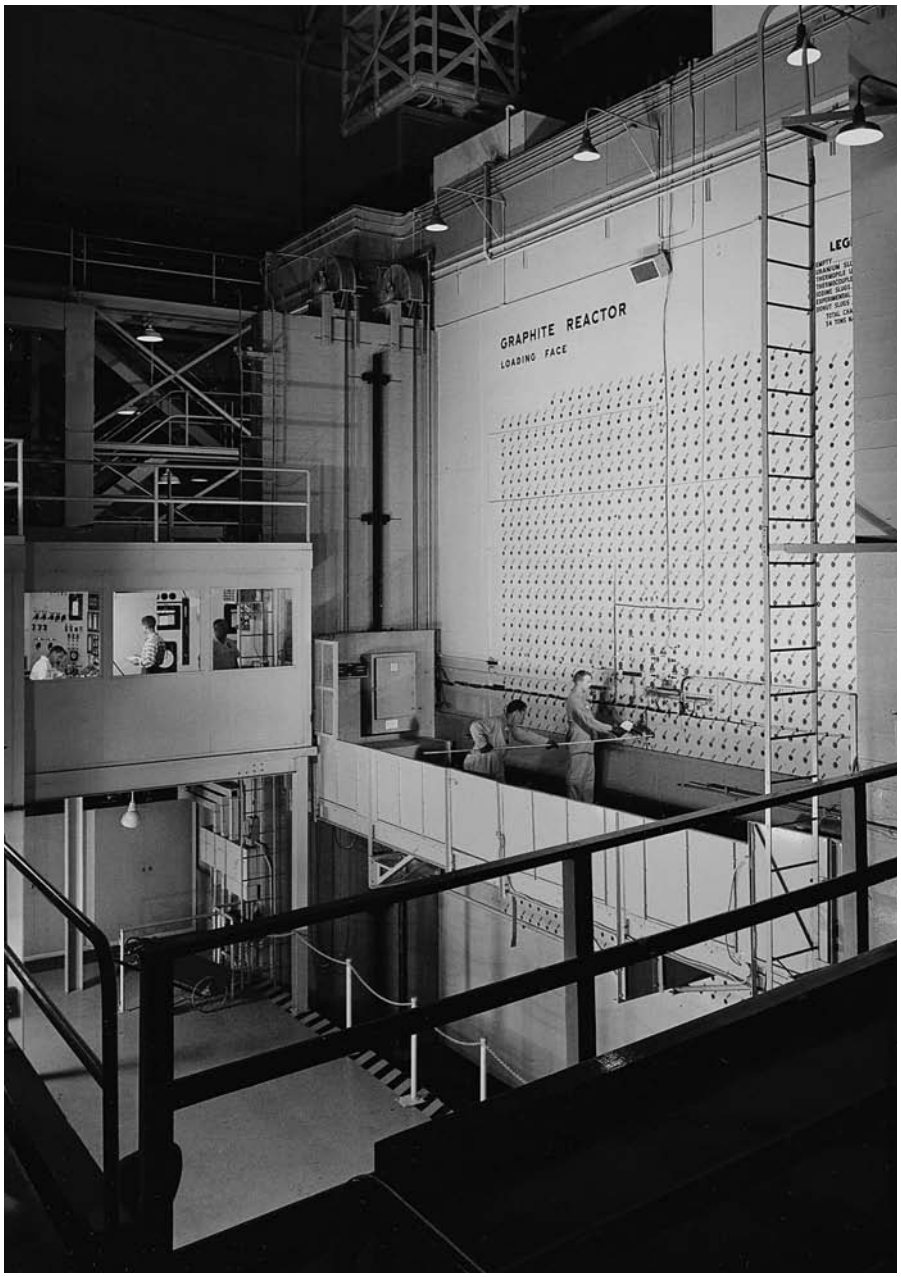


Figure 10.3 Two workers loading uranium slugs into the concrete face of the graphite reactor, X-10, with others in the control room. The photograph in Figure 10.1, of an irradiated sample being removed from the reactor, was on the left side of the reactor, though this shot was taken much later (in the 1960s, perhaps even after the reactor was shut down, in which case the actions were staged). Courtesy Department of Energy Photography.

On August 2, 1946, the day after the Atomic Energy Act was signed into law, Eugene Wigner, the director of Oak Ridge National Laboratory, hand-delivered the first government radioisotope shipment to Edmund Vincent Cowdry and William L. Simpson, research director and associate research director of the Barnard Free Skin and Cancer Hospital, St Louis, Missouri. It was a carefully orchestrated event with full press coverage. The Manhattan Project's civilian successor, the AEC, made the radioisotope program the cornerstone of its program for atomic biology and medicine. From 1946 to 1955, the AEC sent out nearly 64,000 shipments of radioactive materials to laboratories, companies, and hospitals.[17]

The reactor-based production system at Oak Ridge substantially reduced the cost of radioisotopes and dramatically increased their availability. Government officials estimated that whereas the Oak Ridge pile could manufacture 200 millicuries of carbon-14 in a few weeks, at a cost of about $10,000, 'it would take 1,000 cyclotrons to equal this output, and the operating cost would be well over $1,000,000'.[18] The AEC subsidized radioisotope usage in key areas, making radioisotopes ordered for cancer treatment, diagnosis, and research free of charge from 1947.[19] The agency further encouraged laboratory researchers to use radioisotopes by offering courses to scientists on methods for using radioactive materials and by cooperating with industry to make radio-labeled compounds available.

The two isotopes that were shipped from Oak Ridge most frequently – about two-thirds of domestic shipments and a higher proportion of foreign shipments – were phosphorus-32 and iodine-131. Both had been part of medical physics since the 1930s in conjunction with the production of artificial radioisotopes by neutron sources and subsequently by cyclotrons. In both cases, early metabolic studies led rapidly to clinical application.[20] Physicians used phosphorus-32 to treat blood disorders such as leukemia and polycythemia vera, and used iodine-131 to treat hyperthyroidism and, more experimentally, cancer of the thyroid.

Since the 1930s, physicians and scientists had fostered hope that radioisotopes, which could localize to particular tissues, would eventually replace radium and X rays in clinical use to irradiate tumours. The publicity surrounding the government's radioisotope program reinforced this expectation. As one writer for the *New York Times* informed readers, 'properly chosen atoms can become a powerful and highly selective weapon for the destruction of certain types of cancer'.[21] Well into the 1950s, journalists and agency officials perpetuated the mirage that investment in atomic energy would generate cancer cures, an expectation never fulfilled to the extent envisioned.[22] However, this did not mean that radioisotopes proved less useful in clinical application than expected – rather, isotopes became crucial to techniques of visualization for diagnosing diseases, a field of application associated with the term 'nuclear medicine' by the 1950s.

In order to cultivate clinical facilities for medical uses of radioisotopes, the AEC funded research programs and new facilities at a few medical schools, such as UCLA and University of Rochester.[23] The AEC also constructed cancer research hospitals at Argonne and Oak Ridge National Laboratories, referring to one such hospital in 1949 as a 'clinical proving ground'.[24] While these new facilities were being built, the AEC developed an equally significant – and higher volume – clinical venue for the utilization of radioisotopes by working with an already-existing hospital infrastructure, that of the Veterans Administration.[25]

Figure 10.4 Rosalyn Yalow preparing an 'atomic cocktail', 1948. Source: Eugene Straus, *Rosalyn Yalow, Nobel Laureate: Her Life and Work in Medicine,* New York: Plenum Trade, 1998, p. 119. ©1998 Eugene Straus. Reprinted by permission of Basic Books, a member of Perseus Books Group.

The atomic bomb tests at Bikini Atoll in 1946, which went by the name Operation Crossroads, provided motivation for the VA to develop a new kind of radiological expertise.[26] The tests, which involved over 200,000 servicemen, resulted in unanticipated levels of radioactive contamination on the test ships and service vessels.[27] In fact, a third of the three planned tests was cancelled altogether due to the radiological catastrophe caused by the second underwater blast. General Groves and other government officials expressed worry that the men who participated in the Navy's operations at Bikini might bring lawsuits against the government over injuries resulting from their involuntary radiological exposure.[28] In 1947, a newly-created Central Advisory Committee recommended that the VA establish an Atomic Medicine Division to deal with disability claims and other litigation filed by veterans exposed to radiation from atomic bomb testing.[29] The committee envisioned a Radioisotope Program as part of this Atomic Medicine Division, to facilitate 'research aimed at bringing veterans the benefits of medical breakthroughs connected with the use of radioisotopes'.[30] Although the division did not, in the end, materialize, the Radioisotope Program did, beginning with six VA Hospitals establishing Radioisotope Units supplied by the AEC.[31] By 1953, the number of these units had grown to thirty-three, employing 202 staff.[32]

One of the original six units was the Radioisotope Service at the VA Hospital in the Bronx, which, in 1947, hired the young nuclear physicist Rosalyn Yalow to help set up this venture (see Figure 10.4).[33] By 1949, Yalow had established a laboratory there and was investigating the usefulness of radioactive phosphorus and sodium in diagnosing tumours.[34] As she shifted to doing research at the hospital full-time, she was keen to find a physician to collaborate with, and asked Dr Bernard Straus, Chief of Medicine at the hospital, if he had any candidates. He recommended a young clinician named Solomon Berson, who joined Yalow in 1950 after he completed his residency in internal medicine.[35] The two rapidly established a tight partnership in medical research using radioisotopic tracers, beginning with the use of iodine-131 to study thyroid physiology in VA hospital patients.[36] Clinicians began using iodine-131 on a wide scale as soon as the AEC made it available, building on the pre-war record of success in applications of radioiodine to diagnose thyroid function and treat thyroid conditions.[37] Yalow and Berson focused their attention on improving the measurement of iodine-131 clearance rates *in vivo*.

Yalow and Berson extended their use of radioisotopes for precise *in vivo* measurements by tagging erythrocytes with isotopes of potassium and phosphorus to measure blood volume.[38] Like their earlier studies, these investigations relied on being able to inject patients with isotopically labeled materials. Their papers do not include information about the relationship of their research to the treatment and care of these patient-subjects. It is also hard to discern from their publications whether Yalow and Berson regarded their experiments with patients as therapeutic or non-therapeutic. A non-therapeutic research design entails radiation exposure in the absence of any specific medical benefit for the subjects.[39] As we will see, the 'healthy volunteers' invoked in some of their papers provide clear examples of non-therapeutic studies. Equally vague in these publications are the provisions for informed consent. These patient-subjects played a crucial role in Yalow and Berson's research – which in the end, for unexpected reasons, did have important beneficial consequences for endocrinology and medical diagnostics. Most were exposed to very small amounts of radioactivity, primarily iodine-131. Yet the ambiguity as to whether or not these patients were aware of their status and

risks as research subjects, and whether their exposure to radioisotopes was also part of their treatment or diagnosis, remains a troubling aspect of the history, an issue to which I will return.

Within a few years, Yalow and Berson applied their precise methods of measuring blood proteins to see if radioisotopically-labeled insulin disappeared more rapidly from the bloodstream of diabetic than normal subjects. This study put to the test a suggestion by one prominent expert on diabetes that the disease resulted from the abnormally rapid degradation of serum insulin.[40] Yalow and Berson administered radioiodine-labeled insulin to both diabetic and non-diabetic patients as well as to some 'healthy volunteer laboratory personnel' of the VA Hospital in the Bronx.[41] To their surprise, they observed the very opposite of the effect they expected: insulin persisted in the bloodstream of most diabetics far longer than in that of normal subjects. This nullified the rapid degradation theory of diabetes, but it raised another question of why diabetic patients exhibited such a low turnover of insulin in their bloodstream.

Yalow and Berson could differentiate the effects of diabetes from the effects of its treatment with insulin by analyzing another patient population at the hospital: psychiatric patients receiving insulin 'shock therapy'. From the 1930s through the 1960s, psychiatrists in the US used insulin to induce hypoglycemic shock and even coma as a way to treat thousands of schizophrenic patients.[42] Blood samples from two insulin-receiving schizophrenic patients contained the same long-lasting insulin bound to antibody that characterized the insulin-treated diabetic patients. In other words, persistence of insulin in the bloodstream correlated with whether the patient had received exogenous insulin, regardless of their disease (Figure 10.5).[43] Yalow and Berson

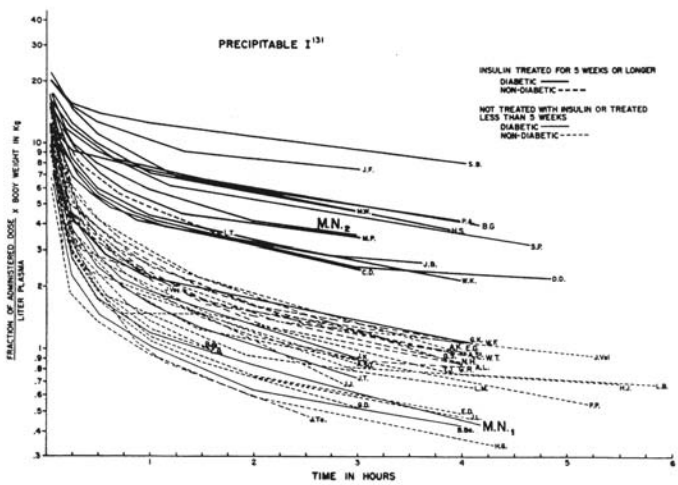
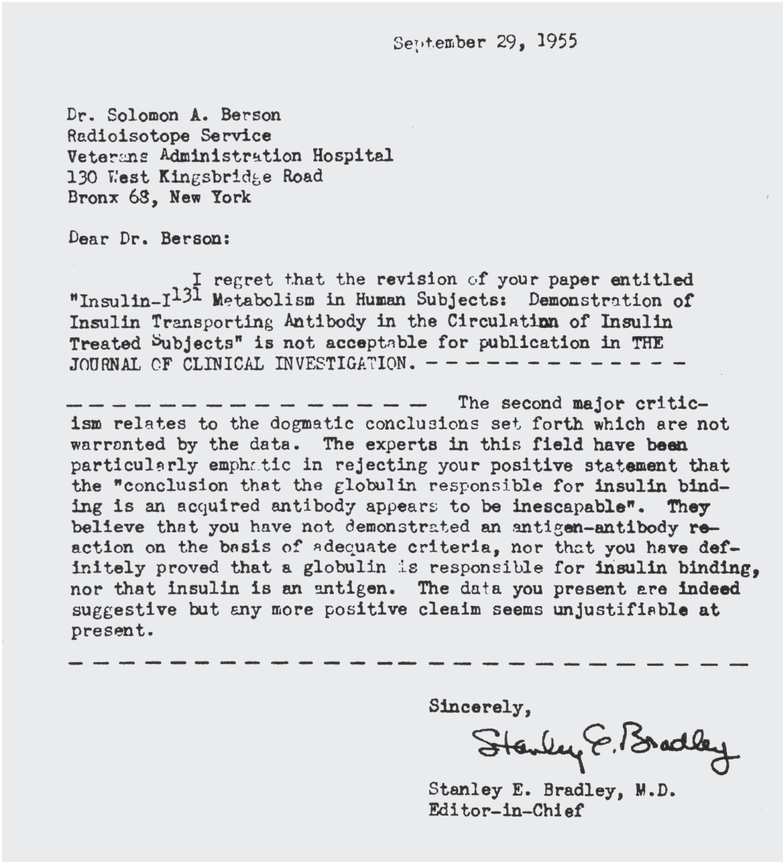


Figure 10.5 'Radioactivity in Plasma as a Function of Time Following Intravenous Administration of Insulin-I-131'. Source: Solomon A. Berson, Rosalyn S. Yalow, Arthur Bauman, Marcus A. Rothschild, and Katharina Newerly, 'Insulin-I^{131} Metabolism in Human Subjects: Demonstration of Insulin Binding Globulin in the Circulation of Insulin Treated Subjects', *Journal of Clinical Investigation*, **35**, 1956, pp. 170–90, at p. 173. Reproduced by permission.

concluded it was the immunogenicity of beef or pork insulin that was responsible for the presence of the insulin-binding antibodies.

Yalow and Berson's contention that patients treated with animal-derived insulin developed antibodies against it was highly controversial. Their manuscripts were rejected from the journal *Science* and initially from the *Journal of Clinical Investigation*, because peer reviewers were not persuaded that a molecule as small as insulin could be immunogenic.[44] As Yalow's biographer states, 'Letters flew back and forth, passion flared, and then, in the midst of the battle, they accepted a compromise to drop the term antibody in the title of the paper and call the protein an insulin-binding globulin'.[45] Yalow's 1977 Nobel Prize address, published in *Science*, included a copy of the letter from the journal of the *Journal of Clinical Investigation*, which laid out the objections to the paper (Figure 10.6).[46]



September 29, 1955

Dr. Solomon A. Berson
Radioisotope Service
Veterans Administration Hospital
130 West Kingsbridge Road
Bronx 68, New York

Dear Dr. Berson:

I regret that the revision of your paper entitled "Insulin-I^{131} Metabolism in Human Subjects: Demonstration of Insulin Transporting Antibody in the Circulation of Insulin Treated Subjects" is not acceptable for publication in THE JOURNAL OF CLINICAL INVESTIGATION. - - - - - - - - - - - -

- - - - - - - - - - - - - - - - The second major criticism relates to the dogmatic conclusions set forth which are not warranted by the data. The experts in this field have been particularly emphatic in rejecting your positive statement that the "conclusion that the globulin responsible for insulin binding is an acquired antibody appears to be inescapable". They believe that you have not demonstrated an antigen-antibody reaction on the basis of adequate criteria, nor that you have definitely proved that a globulin is responsible for insulin binding, nor that insulin is an antigen. The data you present are indeed suggestive but any more positive cleaim seems unjustifiable at present.

- -

Sincerely,

Stanley E. Bradley, M.D.
Editor-in-Chief

Figure 10.6. Excerpts of a letter of rejection received from *Journal of Clinical Investigation*. Source: Rosalyn S. Yalow, 'Radioimmunoassay: A Probe for the Fine Structure of Biologic Systems' (Nobel Lecture for Yalow's 1977 Prize in Physiology or Medicine, shared with R. Guillemin and A. Schally), *Science*, **200**, 1978, pp. 1236–45, at p. 1238. © Nobel Foundation 1977.

In order to overcome this skepticism, Yalow and Berson utilized several physical-chemical techniques to demonstrate that the insulin-binding globulin was a specific antibody, found only in patients who had been treated with exogenous insulin. They used radioelectrophoresis to show that radioactively-labeled insulin migrated with serum gamma globulin (plasma antibodies) in insulin-treated patients. They also employed chromatography and ultracentrifugation to analyze how labeled insulin interacted with serum proteins from patients, both those who had received insulin treatment and those who had not. All the results showed a consistent pattern: in insulin-treated patients most of the radioactivity from labeled insulin was associated with serum gamma globulin protein, that is, IgG antibodies.[47] If the initial reviewers of Yalow and Berson's papers were skeptical, the publications won over the field. Berson received the American Diabetes Association's first Lilly Award in 1957 (Yalow won it in 1961). This was the first of many prizes recognizing their contributions (Figure 10.7).

Figure 10.7 Solomon Berson and Rosalyn Yalow holding the check for the first Eli Lilly Award given by the American Diabetes Association, awarded to Berson in 1957. Source: Eugene Straus, Rosalyn Yalow, *Nobel Laureate: Her Life and Work in Medicine*, New York: Plenum Trade, 1998, p. 153. ©1998 Eugene Straus. Reprinted by permission of Basic Books, a member of Perseus Books Group.

As part of these studies, Yalow and Berson sought to determine the maximum binding capacity of the serum antibodies against insulin.[48] They recognized that the binding of radiolabeled insulin to a fixed amount of antibody is a quantitative function of the amount of insulin present. When a small amount of radioactively-labeled insulin was added to insulin antibody, all of it was bound by the antibody. The addition of unlabeled insulin prevented the binding of labeled insulin in proportion to the total amount of insulin present. This meant that one could add labeled insulin to a solution containing both insulin antibody and an unknown amount of insulin, and calculate precisely the concentration of insulin based on how much of the labeled insulin was bound by antibody (Figure 10.8). This is the principle of radioimmunoassay, although it was three more years before Yalow and Berson published a paper showing how the technique could be used to measure insulin levels in human plasma.[49] Their method for determining insulin concentration relied on several assay points; one could compare the curve of bound to free insulin to a curve using known standards. Yalow and Berson claimed that their technique could measure human insulin down to a range of 0.25–1.0 μ-units (1.25–5.0 μ-units per milliliter). The sensitivity of this method improved upon existing bioassay techniques by about two orders of magnitude, and enabled users to measure levels of human serum insulin directly using a very small amount of blood.[50]

The Technological Trajectory of Radioimmunoassay

Yalow and Berson were not the only investigators to realize that competitive binding, radioactive labels, and specific antibodies could be used in concert for quantitative assays. In the UK, Roger Ekins was working in the Department of Physics Applied to Medicine at the Middlesex Hospital Medical School in London. He was collaborating with some hormone biochemists on developing assay techniques for serum thyroxine

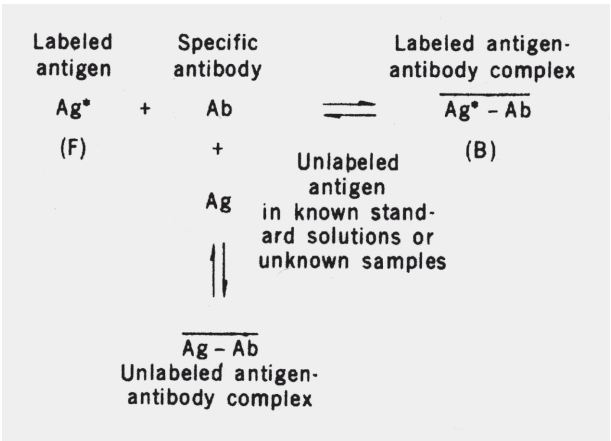


Figure 10.8 Schematic diagram showing the competing reactions that form the basis of radioimmunoassay (RIA). Source: Rosalyn S. Yalow, 'Radioimmunoassay: A Probe for the Fine Structure of Biologic Systems' (Nobel Lecture for Yalow's 1977 Prize in Physiology or Medicine, shared with R. Guillemin and A. Schally), *Science*, **200**, 1978, pp. 1236–45, at p. 1239. © Nobel Foundation 1977.

(thyroid hormone), and realized that the recently isolated specific thyroxine-binding globulin (antibody) and radio-labeled hormone could be used for the purpose of such an assay. As he has recounted since, his idea was greeted with skepticism by his peers and he was refused funding to purchase the radiolabel needed to test it. However, in 1957 a hospital patient provided him with the opportunity to follow up this idea. The patient had a thyroid tumor and was being treated with massive doses of iodine-131. Ekins observed that the resulting radioactivity in the patient's bloodstream was largely bound by blood proteins – specifically, antibodies to the patient's now-radioactive thyroid hormone – and Ekins used blood samples from this patient to show how unlabeled exogenous thyroid hormone could compete with the radioactive endogenous thyroxine bound to serum antibody.[51] As in the case of Yalow and Berson's work, the postwar use of radioisotopes, especially radioiodine, in clinical medicine provided the context in which the radioimmunoassay method took shape.[52] Both the antigens being studied – insulin and thyroxine – were hormones. A third research group developed a radioimmunoassay for another hormone, glucagon, in 1959.[53]

Through the late 1960s, endocrinology remained the major arena of application for radioimmunoassay (Figure 10.9).[54] Yalow and Berson extended their method to develop assays for a variety of other peptide hormones including growth hormone, ACTH, parathyroid hormone, and gastrin.[55] This research direction took advantage of the fact that many peptide hormones were newly available in pure form. Non-peptide hormones, beginning with thyroxine, were also targeted – the development of radioimmunoassays for steroids being especially notable.[56] These assays benefited medical practice as well as research: being able to detect various hormones in human plasma down to picomolar concentrations (a trillionth of a mole) greatly expanded the diagnostic capabilities of clinical endocrinology.[57] In fact, it brought many blood hormones within range of direct measurement – hormones such as insulin and thyroxine were not concentrated enough

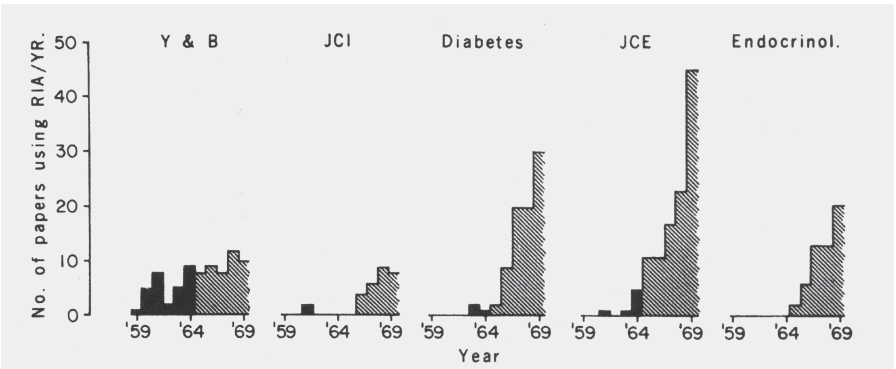


Figure 10.9 'Number of papers concerning experiments in which RIAs were used published by Yalow and Berson (Y and B, left) and all others in American journals of endocrinology and diabetes through 1969. Papers before 1965 are shown in black; 1965 and later are cross-hatched. (JCI, *Journal of Clinical Investigation*; JCE, *Journal of Clinical Endocrinology*; Endocrinol., *Endocrinology*). Source: Rosalyn S. Yalow, 'Radioimmunoassay: A Probe for the Fine Structure of Biologic Systems' (Nobel Lecture for Yalow's 1977 Prize in Physiology or Medicine, shared with R. Guillemin and A. Schally), *Science*, **200**, 1978, pp. 1236–45, at p. 1239. © Nobel Foundation 1977.

for detection by the antibody-based agglutination tests of the 1950s. At the same time, the new detection methods led researchers to recognize that many hormones (nearly all peptide hormones) exist in more than one form *in vivo*, due to the presence of precursors and metabolic products. Many hormone precursors, such as pro-insulin and big gastrin, were identified and characterized through use of radioimmunoassay in concert with other methods of analysis, such as electrophoresis. Thus the increasing sensitivity of immunoassays was accompanied by a growing recognition of the actual heterogeneity of the target molecules.[58]

This sophisticated detection method relied on a very old-fashioned substance, anti-sera from laboratory animals, as its source of antibodies. In Yalow and Berson's laboratory, the anti-sera came from guinea pigs, each of which was inoculated with a distinct antigen, such as gastrin or growth hormone. Yalow's biographer writes that in the early hours of the morning, she would spend time with her guinea pigs, offering them lettuce from home, cradling them in the crook of her arm, and cajoling them to produce the best anti-sera in the world (Figure 10.10).[59] Her laboratory did not make its valuable anti-sera available for sale, but it did provide precious vials to the scientists who came from all over the world to the Bronx to learn its methods.

Figure 10.10. Rosalyn Yalow holding one of the anti-sera-producing guinea pigs in her laboratory. Source: Eugene Straus, *Rosalyn Yalow, Nobel Laureate: Her Life and Work in Medicine*, New York: Plenum Trade, 1998, p. 15. ©1998 Eugene Straus. Reprinted by permission of Basic Books, a member of Perseus Books Group.

In the early 1970s, radioimmunoassays began to reach a much wider range of users – and began to go by the acronym RIA. The emergence of commercial radioimmunoassay reagents and 'kits' registered and reinforced this trend, while taking advantage of new technical developments. In particular, iodine-125 overtook iodine-131 as the label of choice, and the longer half-life of this isotope in turn meant a reasonable shelf life for commercial assay kits.[60] New England Nuclear, which had been founded in 1956 to provide radio-labeled reagents to researchers, moved into the area of radioimmunoassay products and featured this technique in their 1973 Annual Report.[61] Their report focused on the uses of RIA for endocrine diagnosis (e.g., for pituitary hormones to diagnose various endocrine disorders and for angiotensin I, whose levels were affected by hypertension) and drug dosage (e.g., for digoxin or digitoxin in patients with congestive heart failure) (Figure 10.11).[62] Yalow and Berson and their colleague J.H. Walsh developed a radioimmunoassay for hepatitis-associated antigen in 1970, and by the end of the decade this became the 'method of choice for testing for infected blood in Red Cross and other blood banks in the United States'.[63] One writer has gone so far as to credit government regulation requiring blood banks to screen for hepatitis with fostering the commercial development: 'RIA was the only method with the required sensitivity at that time. And Abbott Diagnostic was the only company with a suitable

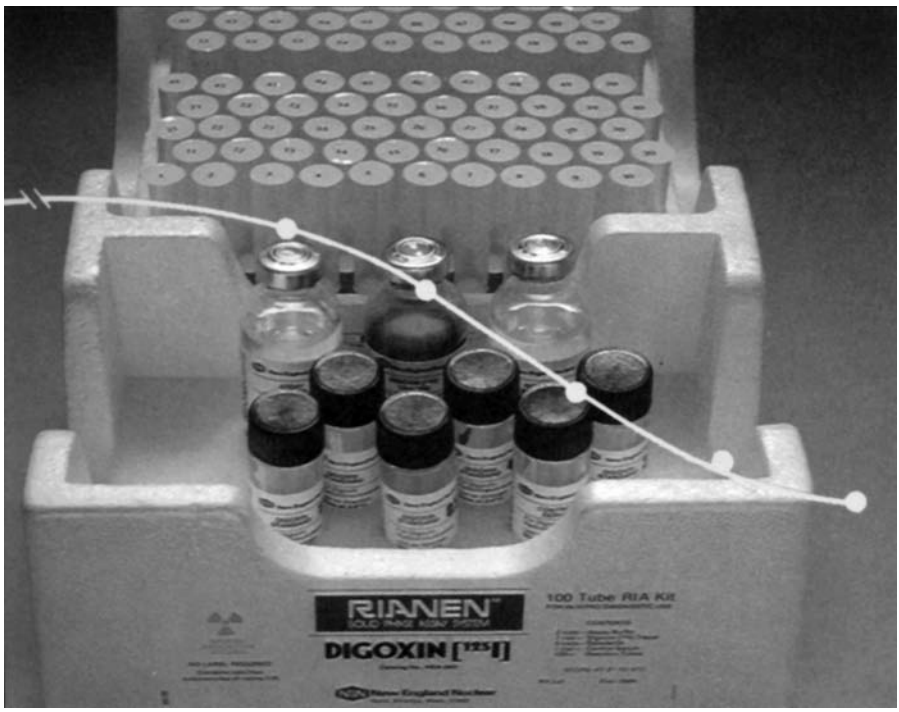


Figure 10.11. Picture of a Digoxin ^{125}I radioimmunoassay kit from New England Nuclear. 'To provide data necessary to evaluate, monitor, and improve the management of digitalized patients, NEN provides the Digoxin ^{125}I RIA kit. A typical "standard curve," from which a patient's digoxin level might be determined, overlays the photo'. Source: New England Nuclear 1977 Annual Report, courtesy of Paul McNulty.

RIA'.[64] Oncology was another growing market for RIA-based *in vitro* diagnostics, since patients could be screened for antigens that marked particular tumours, especially endocrine tumours, either to enable early detection or to monitor cancer patients after treatment.[65] In the late 1970s, RIA diagnostic tests for carcino-embryonic antigen and for hepatitis comprised about 20 per cent of the commercial market.[66] RIA attained an impressive scale of use: around fifty-two million radioimmunoassays were performed in 1975.[67]

In effect, the movement of RIA, in the 1970s, from research laboratories to clinical laboratories necessitated the industrialization of the technique. As one commentator described the situation in 1979,

> The clinical diagnostic laboratory industry is large, growing, and highly fragmented. Many people fail to realize that the clinical laboratory industry generates approximately $10–12 billion in revenues per year and is approximately the same size as the ethical drug industry. There are approximately 7,000 hospital laboratories which generate approximately $5 billion, and approximately 7,000 independent commercial laboratories which generate another $2.5 billion per year. In addition, there are 50,000–60,000 physician office laboratories which perform some $2.5 billion worth of testing. . .
>
> Basically, there's logistics – how do you get 17,000 samples picked up from 8,000 doctors? Sample handling – how do you number in 17,000 patients properly? If we put the wrong number on the wrong patient, and give someone else leukemia, we do not keep that account very long. Production – how do we get the correct answer on 256,000 tests each day? Reporting – how do we produce the reports on an overnight basis, and transmit them back to the 30 cities? How do we bill 8,000 clients and now with the New York Patient Billing Law and the Rhode Island Patient Billing Law, how do we bill 160,000 patients every single month in amounts from $5.00 to $15.00?[68]

One answer to the challenge of scaling up the use of RIA for *in vitro* diagnostics was the development of automated instrumentation. By 1979, there were six automated systems available. Beyond the labor-saving advantages of automation, these instruments also helped minimize exposure of workers in high-volume testing laboratories to the radioactivity of the samples.[69]

In 1975, Georges Köhler and César Milstein published their method for the *in vitro* synthesis of monoclonal antibodies, antibodies against single antigen binding sites or epitopes, produced from cultured cells. The individual antibody-producing cells, or B lymphocytes, are fused with tumour cells to allow their propagation by cell culture; the clonal lines created by this technique are referred to as hybridomas. By contrast, ordinary polyclonal antibodies are generated by many different lineages of B lymphocytes, each of which produced a specific antibody against one of many binding sites on the antigen.[70] Monoclonal antibodies thus provided two striking advantages in antibody-based detection techniques: they offered enhanced specificity because they were completely homogeneous in their binding of antigen, and they circumvented the reliance on animals for antibodies in anti-sera. The monoclonal 'revolution', however, did not occur immediately. Ekins has called attention to the lag of nearly a decade between Köhler and Milstein's publication and the use of monoclonal antibodies in immunoassays.[71] In accounting for this delay, Alberto Cambrosio and Peter Keating argue that a great deal of art and effort was required to replicate hybridoma technology

in order to scale up the production of monoclonal antibodies, even after the initial techniques had been published.[72] Monoclonal antibodies were costly to produce. Even so, by the late 1980s, human and veterinary diagnostic tests using monoclonal antibodies represented the vast majority of biotech products on the market.[73]

Since the 1980s, growing concerns about the health effects of low-level radiation exposure as well as stricter regulations for disposal of radioactive waste have provided incentives for laboratories to shift to non-radioactive labels in immunoassays – such as enzymatic, chromogenic, fluorescent, and luminescent tags.[74] In commercial assay kits, non-isotopic labels tend to have a longer shelf life than radiolabels. Nonetheless, radioimmunoassay has not become an obsolete technology. As one observer noted in 1979, 'The demise of RIA as a technology for sensitive assays has been discussed almost since it was introduced'.[75] One science writer has attributed the enduring utility of RIA to its tremendous sensitivity, part of which derives from the nature of radioactivity as a label, with which one can potentially detect even a few tagged molecules.[76] As of 1994, there were at least forty-four commercial suppliers of radioimmunoassay kits, reagents, and supplies.[77] Clinical laboratories were still using RIA to measure levels of substances such as 'pregnancy and growth hormones, drugs ingested therapeutically or illegally, such as antibiotics, cocaine, and steroids; antigens that are characteristic of autoimmune thyroid disease and other autoimmune disorders and antigens that indicate infection by various bacteria, parasites (such as schistosoma), and viruses'.[78]

Workplace testing for drugs has become a significant facet of the commercial immunoassay market, particularly after President Reagan's executive order in 1986 'directing federal agencies to achieve a drug-free federal workplace'.[79] Forensic toxicologists had already begun to develop sensitive drug tests before Reagan's mandate. Among the methods that came to market in the early 1980s was a radio-labeled assay for drug testing called Abusescreen. According to the National Institute of Drug Abuse (NIDA) guidelines for employee drug testing, developed in the late 1980s, two different analytical methods should be used to reach a positive result: initial screening by immunoassay, and confirmation by gas chromatography/mass spectrometry.[80] Usually enzyme-linked immunoassays are used for the initial screening, although the US military, which has more stringent regulations than the NIDA guidelines, requires more sensitive tests using RIA.[81]

In the 1990s, the frontier for immunoassays, including RIA, became environmental monitoring and toxicology. Targeted compounds have included halogenated hydrocarbons such as polychlorinated biphenyls (PCBs) and dioxins, dichloro-diphenyl-trichloroethane (DDT), herbicides such as atrazine, and a wide variety of other pollutants and contaminants.[82] As one observer notes, 'developing antibodies to toxic chemical haptens comes with its own set of problems', not least that if one is using an animal to provide the antibodies, it may not be able to survive injection with such poisonous compounds.[83] In addition, other analytical methods have their own advantages. Traditional chromatographic methods of environmental monitoring, although costly, allow analytical chemists to detect multiple residues, a feature only recently developed for immunoassays.[84] On the other hand, the sensitivity of immunoassays exceeds most rival methods, and the technology has already been developed for high-volume sample processing. One government research group adapted an RIA from medical diagnostics to develop a sensitive screen for the presence of antibiotics shed from confined livestock

operations into ground water.[85] Immunoassays have also been used to test for the presence of pesticide-based metabolites in humans.[86] The advancing threshold of detection for agrochemicals and pollutants is a concern for industry. As one commentator has noted, government regulations tend to 'parallel the sensitivity of the detection technologies', whether or not such levels are linked to health risks.[87]

Thus antibody-based assay methods have expanded beyond the arena of clinical diagnostics to be used by companies and federal agencies in the monitoring of certain morally-charged chemical compounds, which can now be detected at a few parts per billion. The state makes use of these technologies in its efforts to compel individuals, institutions, and companies to comply with government regulations, whether in the name of a drug-free workplace, a safe blood supply, or an uncontaminated environment. These efforts by the government to monitor individuals and ecosystems do not go uncontested.[88] RIA, having originated in the atomic age, helped make possible a world of molecular surveillance.

Concluding Reflections: Atomic Guinea Pigs?

This study of the development of radioimmunoassay is one thread of a larger project on the origins and consequences of the US Atomic Energy Commission's radioisotope distribution program.[89] The AEC program provided physicians with radioisotopes for therapy, diagnosis, and research and equipped scientists in a variety of fields to address longstanding questions in new ways. Radioisotopes found wide-ranging uses, especially in biology. Biochemists used them as molecular tracers in the visualization of intracellular processes from photosynthesis to glycolysis. Ecologists used them to trace the circulation of phosphorus and other elements through ecosystems.[90] The technique of radioimmunoassay similarly took advantage of this new mode of visualizing molecules, in this case to identify and quantify antigens with unrivaled sensitivity. Radioimmunoassay thus extended the capability of scientists to access previously unseen molecular agents, demonstrating the power of radiolabels in technologies for detection and diagnostics.

Ernst F. Pfeiffer, a distinguished diabetes researcher, has singled out radioimmunoassay as evidence of the 'impact of insulin research upon biomedicine and clinical application'.[91] As he suggests, the development of RIA challenges the commonly-held notion that biomedical knowledge is born in basic research laboratories and applied in clinics, for this antibody-based detection technique emerged from a scientific finding made in the clinical realm, and then was adopted by a wide array of basic researchers – both within and beyond biomedicine – even as it generated new diagnostic tools for clinical practice. This example is by no means unique in showing the complex pathways through which biomedical findings and technologies circulate between 'bench and bedside'; historians of medical research have been pointing to the clinic as a source of scientific innovation for some time.[92] Nonetheless, the case of RIA makes the point especially vivid.

At the same time, it is worth asking *why* radioimmunoassay emerged from clinical experiments and observations, since there is no reason that techniques using competitive antibody binding need have originated in a research hospital. The answer necessarily implicates the US AEC, which not only made radioisotopes available and affordable, but strongly encouraged clinicians to experiment with them. The government's push to reap medical dividends from the atomic age did catalyze impressive innovations in

nuclear medicine, but the human experimentation that enabled these advances has come under public criticism during the last fifteen years.[93] In 1993, investigative journalist Eileen Welsome first published reports naming Americans who had been injected with plutonium, many without being informed, much less asked to consent.[94] Her stories spurred other reporters to uncover incidents of government-sponsored radiation experiments on patients, pregnant women, and children. Responding to intense public pressure and outrage, the US government admitted in December 1993 to having concealed human radiation experiments.[95] President Clinton subsequently appointed an Advisory Committee on Human Radiation Experiments early in 1994, and they published a report in 1995.[96] The committee sought to bring the government record on these matters to light, where there was a record – for the documents concerning human experiments were incomplete even where declassified.

In their report, the Advisory Committee points out that, so far as the AEC's radioisotope distribution program was concerned, the agency was attuned from the beginning to the need for ethical oversight for human uses. Beginning in 1946, a Subcommittee on Human Application of the Interim Advisory Committee on Isotope Distribution Policy reviewed, with veto power, any requests for radioactive materials to be used in humans. By October 1946, there were 217 requests, 211 of which had been approved. 94 of these 217 requests were for human usage; 90 of them were approved.[97] Initially, the main ethical concern of the committee was allocation – since radioisotopes were still regarded as a scarce resource, this committee was charged with setting priorities, both among various possible human uses and between human uses and research applications. However, as the Oak Ridge facility increased production, supply kept up with demand – and in fact exceeded it. In retrospect, the ethics of allocation appear much less significant than issues of safety and informed consent. Although the AEC acknowledged the importance of consent from the spring of 1947, the agency did not develop a consent requirement for experimental volunteers until the late 1950s. In general, local committees at institutions that received AEC radioisotopes were expected to monitor radiation hazards and safeguard patients.[98]

Clinton's Advisory Committee pointed to the development of radioimmunoassay by Yalow and Berson as an example of the unexpected and beneficial consequences from experimentation – in this case, clinical experimentation – using radioisotopes.[99] Yet the broader legacy of the Manhattan Project and the AEC illustrates how the government's sense of urgency in developing atomic energy, first for new weapons then for civilian application, ran ahead of scientific understanding of the hazards of exposure – and sometimes ahead of protection against known dangers. In formulating guidelines to protect scientists, physicians, patients, and workers exposed to radioisotopes as well as other sources of radiation, the AEC drew on existing frameworks for safety and permissible exposure developed by health physicists in the Manhattan Project and by the non-governmental National Committee on Radiation Protection, the latter of which had been first established in 1929 in response to injuries and deaths from X rays and radium.[100] Assessing and mitigating the adverse effects of the newly available radioisotopes was difficult, because the specific risks associated with exposure to most reactor-produced radioisotopes were unknown – many of these artificial radioisotopes had not been previously produced in such large quantities if at all.[101] The AEC emphasized safe handling and disposal of radioactivity in its isotope distribution program, requiring

the institutions licensed to receive its isotopes to abide by its guidelines, though it is not clear how these were enforced. Officials and scientists tended to assume that the dangers of low-level radiation exposure, such as that usually associated with tracer uses of isotopes, were too minimal to warrant much concern. However, critics, both at the time and since, questioned whether the agency's emphasis on promoting atomic energy and advancing atomic weaponry hindered full disclosure of radiation risks and compromised the safety of users and experimental subjects.

Two sets of non-therapeutic human experiments with radioisotopes brought to light in the 1990s attracted particularly strong criticism and, in one case, litigation. The first was a study of the nutritional needs of pregnant women undertaken by the Tennessee Department of Health and researchers at Vanderbilt Medical School, with funds from the Public Health Service and the Rockefeller Foundation. One part of the study addressing iron absorption during pregnancy involved oral ingestion of tracer amounts of radioiron by 'approximately 820 poor, pregnant Caucasian women'.[102] Researchers drew blood from these pregnant subjects on their subsequent prenatal visit to analyze the percentage of iron absorbed, and measured the radioactivity of the iron in their infants at birth. Although the scientific question prompting the investigation was legitimate – anemia during pregnancy is a commonplace problem – the radioactive iron offered no benefit to the pregnant subjects, and whether the doses carried risk to their fetuses has been a matter of study and debate since the 1960s. The Advisory Committee stated that they found 'some indication that the women neither gave their consent nor were aware they were participating in an experiment'.[103] In 1998, a class action lawsuit on behalf of these women resulted in a $10.3 million settlement.[104]

Non-therapeutic studies were also conducted on institutionalized children. Most notably and notoriously, nutritional researchers from MIT fed cereal containing trace amounts of radioactive iron and calcium to 'students at the Walter E. Fernald School, a Massachusetts institution for mentally retarded children'.[105] The study was funded by the Atomic Energy Commission, the National Institutes of Health, and Quaker Oats Company. The young male subjects were members of the school's 'science club,' and they were offered treats for participating such as extra milk and special outings. The Advisory Committee on Human Radiation Experiments singled this study out for its ethical problems, even by standards of the time.[106]

Alongside the pregnant women and children who have become conspicuous for their roles in radioisotope experiments, veterans occupy a distinct historical position as subjects of investigation. In the US, soldiers and veterans served as 'scientific guinea pigs' in two kinds of activity related to atomic energy. First and foremost, military personnel were unwitting subjects in the dozens of atomic test explosions that took place between 1946 and 1963.[107] To the degree that the planners of these tests regarded military personnel as human subjects, these studies were designed to investigate not the biological effects of radiation, but the psychological and physiological reactions of servicemen to the atomic blasts. These research subjects, often involved in training maneuvers at test sites, formed a small contingent of the 200,000 people who experienced radiation exposure in conjunction with American atomic weapons testing. Servicemen who experienced radiation as an occupational hazard at test sites were still used as sources of biomedical data.[108] In the 1960s and 1970s, hundreds of veterans who participated in nuclear tests filed claims with the Veterans Administration for service-connected radiation injuries.[109]

Although the VA ruled in favor of only a handful of claimants, the veterans' cause became a political issue. In 1988, Congress passed legislation establishing compensation for radiation-exposed veterans irrespective of whether injury could be proven.

The other arena of exposure related to military service was strictly clinical: as we have seen, veterans were at the front-lines of medical experiments with radioisotopes at VA Hospitals in the late 1940s and 1950s. The AEC took advantage of the government-controlled hospital infrastructure for military personnel in order to establish clinical research sites for nuclear medicine. This meant that veterans were in a position to benefit from the most recent advances in nuclear medicine, but they were also part of the AEC's clinical proving ground for radioisotopes. The government's motivation in this case was not so much military as political – the agency was eager for medical breakthroughs that would demonstrate atomic energy's peaceful uses in the midst of an emerging nuclear arm race.

Although RIA could have been developed without the use of human subjects, both in the US and the UK the novel binding assays arose as part of clinical research programs where patients were being treated with radioisotopes. In effect, human subjects and patients were the experimental vessels for observing competitive binding behavior of antibodies in the presence of marked antigen. Yalow herself emphasized the serendipitous nature of RIA, emerging as it did from her studies of insulin metabolism in a hospital's Radioisotope Service.[110] Yalow and Berson's subsequent development of a laboratory technique from these initial observations effectively replaced the human body – which was both the site for binding reactions and the source of antibodies – with test tubes on the one hand, and animal sera on the other. In the 1980s, antibodies synthesized *in vitro,* that is, monoclonal antibodies, began replacing animal-derived antibodies. The trajectory of technological development was one of *disembodiment*, a progressive liberation from dependence on diabetic veterans, and then actual guinea pigs, to become an automated process using purely synthetic constituents. Or to put it another way, RIA externalized clinical observations, rendering what had been an *in vivo* experiment into an *in vitro* assay. This examination of the technique's history has put the veterans and guinea pigs back into the picture, to elucidate the complex legacies of government atomic energy policy and clinical research for postwar immunology.

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Notes

1 Peter Keating and Alberto Cambrosio have published extensively on the development of other immunologically-based tools and techniques, such as monoclonal antibodies, immunophenotyping, and flow cytometry. See Alberto Cambrosio and Peter Keating,

Exquisite Specificity: The Monoclonal Antibody Revolution, New York: Oxford University Press, 1995; Peter Keating and Alberto Cambrosio, *Biomedical Platforms: Realigning the Normal and the Pathological in Late-Twentieth-Century Medicine*, Cambridge, MA: MIT Press, 2003.

2 ELISA is an acronym for Enzyme-Linked ImmunoSorbent Assay. The method continues to be widely used clinically, particularly in testing for antibodies to HIV (Human Immunodeficiency Virus).

3 On the longer history of immuno-diagnosis, see Arthur M. Silverstein, *A History of Immunology*, San Diego, CA: Academic Press, 1989, pp. 305–25.

4 Albert Q. Maisel, 'Medical Dividend', *Collier's*, **119**, 1947, pp. 43–4.

5 This number represented a doubling of the number from the 1973 and 1974 national surveys. Bennett Zucker, 'What's Right and Wrong with RIA', *Laboratory Management*, **14**, 1976, pp. 35–8.

6 To prepare a Western blot, the researcher separates proteins by gel electrophoresis, transfers the proteins from the polyacrylamide gel to a filter membrane, on which they are immobilized, and then uses labeled antibodies to identify proteins of interest.

7 Rosalyn S. Yalow, 'Citation Classics Entry', *Current Contents*, *Life Sciences*, **14**, 1977, p. 98. Yalow shared the Nobel Prize with peptide biochemists Roger Guillemin and Andrew Schally.

8 On the 'physicists' war', see Daniel J. Kevles, *The Physicists: The History of a Scientific Community in Modern America*, New York: Knopf, 1977.

9 Evelyn Fox Keller, 'Physics and the Emergence of Molecular Biology: A History of Cognitive and Political Synergy', *Journal of the History of Biology*, **23**, 1990, pp. 389–409; Evelyn Fox Keller, *Secrets of Life, Secrets of Death: Essays on Language, Gender and Science*, New York: Routledge, 1992, pp. 39–55.

10 The trend among historians of science to attribute the 'revolution in biology' to physicists goes back to Donald Fleming, 'Émigré Physicists and the Biological Revolution', *Perspectives in American History*, **2**, 1968, pp. 152–89. Like many truisms, this historical explanation disintegrates under close scrutiny. Rasmussen provides an excellent analysis of the historiography connecting the emergence of molecular biology to physics: Nicolas Rasmussen, 'The Mid-Century Biophysics Bubble: Hiroshima and the Biological Revolution in America, Revisited', *History of Science*, **35**, 1997, pp. 245–93. Soraya de Chadarevian analyzes postwar British developments along similar lines as Rasmussen, arguing that atomic energy-related funding for biophysics was crucial to establishing the Unit for the Study of Molecular Structure of Biological Systems at Cambridge. In the 1950s this laboratory became the first institution to use the name Molecular Biology, even as the connections to atomic energy were progressively less visible. Soraya de Chadarevian, *Designs for Life: Molecular Biology after World War II*, Cambridge: Cambridge University Press, 2002. My comments on physicists, atomic energy, and postwar biology draw on a historiographical overview that I co-authored with María Jesús Santesmases: 'Radiobiology in the Atomic Age: Changing Research Practices and Policies in Comparative Perspective.' *Journal of the History of Biology*, **39**, 2006, pp. 637–47.

11 Alice Kimball Smith, *A Peril and a Hope: The Scientists' Movement in America, 1945–47*, Chicago: University of Chicago Press, 1965.

12 See Stuart M. Feffer, 'Atoms, Cancer, and Politics: Supporting Atomic Science at the University of Chicago, 1944–1950', *Historical Studies in the Physical and Biological Sciences*, **22**, 1992, pp. 233–61; Peter J. Westwick, 'Abraded from Several Corners: Medical Physics and Biophysics at Berkeley', *Historical Studies in the Physical and Biological Sciences*, **27**, 1996, pp. 131–62;

David S. Jones and Robert L. Martensen, 'Human radiation experiments and the formation of medical physics at the University of California, San Francisco and Berkeley', in Jordan Goodman, Anthony McElligott and Lara Marks (eds), *Useful Bodies: Humans in the Service of Medical Science in the Twentieth Century,* Baltimore, MD: Johns Hopkins University Press, 2003, pp. 81–108.

13 For more on Lawrence and cyclotron-produced radioisotopes, see J.L. Heilbron and Robert W. Seidel, *Lawrence and His Laboratory: A History of the Lawrence Berkeley Laboratory*, Berkeley, CA: University of California Press, 1989, pp. 395–414. I give a fuller account of the collaborations between cyclotron physicists and life scientists, particularly biochemists, but also physicians, in Angela N.H. Creager, 'Nuclear Energy in the Service of Biomedicine: The US Atomic Energy Commission's Radioisotope Program, 1945–1950', *Journal of the History of Biology*, **39**, 2006, pp. 649–84.

14 S. Hertz, A. Roberts, and Robley D. Evans, 'Radioactive Iodine as an Indicator in the Study of Thyroid Physiology', *Proceedings of the Society for Experimental Biology and Medicine*, **38**, 1938, pp. 510–13; Clark T. Sawin and David V. Becker, 'Radioiodine and the Treatment of Hyperthyroidism: The Early History', *Thyroid*, **7**, 1997, pp. 163–76.

15 To borrow a metaphor from the AEC, labeling a molecule with a radioactive tracer atom is like putting a bell on a sheep – you can find it wherever it goes, even when it is hidden. There is an image with the caption 'flocks of sheep are traced by individual sheep with bells' in National Archives, College Park, MD, photograph AEC-62 6611, 434-SF-86-52. Radioisotopic tracers were used in the physical sciences as well, but my analysis focuses on their biological and medical applications. See Martin D. Kamen, *Radioactive Tracers in Biology: An Introduction to Tracer Methodology*, New York: Academic Press, 1949.

16 Manhattan Project, 'Availability of Radioactive Isotopes', *Science*, **103**, 1946, pp. 697–705, at p. 697.

17 United States Atomic Energy Commission, 'Introduction', *Eight-Year Isotope Summary*, *vol. 7* of *Selected Reference Material, United States Energy Program*, Washington, D.C.: US Government Printing Office, 1955, p. 2. Because many shipments were bulk amounts going to companies that prepared radio-labeled compounds and radiopharmaceuticals, this number underestimates the actual number of shipments received at end destinations. As stated in this source, 'The total number of isotope shipments received by ultimate users is several times greater than the quoted number of shipments [63,990] from ORNL [Oak Ridge National Laboratory]'. At the time of the first shipment, the facility was known as Clinton Laboratories; it was christened Oak Ridge National Laboratory in 1949.

18 US Atomic Energy Commission, *Fourth Semiannual Report*, as quoted in 'Investigation into the United States Atomic Energy Project', Hearings Before the US Congress Joint Committee on Atomic Energy, 81st Congress, Part 7, 13 June 1949, p. 291. The original actually reads 'a hundred million dollars', which may be an error.

19 US Atomic Energy Commission, *Sixth Semiannual Report*, Washington, D.C.: US Government Printing Office, 1949, pp. 90–101.

20 For more detail on the early applications and postwar uses of phosphorus-32 and iodine-131, see Creager, 'Nuclear Energy in the Service of Biomedicine' (n.13).

21 Harry M. Davis, 'The Atom Goes to Work for Medicine', *New York Times Magazine*, 22 September 1946, p. SM8. Also quoted by the Advisory Committee on Human Radiation Experiments, *The Human Radiation Experiments: Final Report of the President's Advisory Committee*, New York: Oxford University Press, 1996, p. 173.

22 Radiation therapy was already an important part of cancer treatment in the 1930s, and it has continued to be used to the present day. The AEC's program did usher in new radioactive sources, such as cobalt-60, but the hope that specific radioisotopes could be administered internally to target particular kinds of tumours was not realized, except insofar as iodine-131 could be used to treat thyroid cancer.

23 See Timothy Lenoir and Marguerite Hays, 'The Manhattan Project for Biomedicine', in Philip R. Sloan (ed.), *Controlling Our Destinies: Historical, Philosophical, Ethical, and Theological Perspectives on the Human Genome Project*, Notre Dame, IN: University of Notre Dame Press, 2000, pp. 29–62.

24 US Atomic Energy Commission, *Sixth Semiannual Report* (n.19), p. 91.

25 During the same time period that VA Hospitals provided key sites for the development of clinical uses of radioisotopes, they were similarly important to the emergence of clinical trials. Harry M. Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990*, Cambridge: Cambridge University Press, 1997.

26 Advisory Committee, *Human Radiation Experiments* (n. 21), pp. 299–300.

27 See Jonathan M. Weisgall, *Operation Crossroads: The Atomic Tests at Bikini Atoll*, Annapolis, MD: Naval Institute Press, 1994.

28 As it turned out, such lawsuits did not materialize until much later; see the last section of this essay as well as Weisgall, *Operation Crossroads* (n. 27), pp. 275–8.

29 In their account, the US Advisory Committee mentions that the 'Central Advisory Committee' advised the VA to keep the creation of the Atomic Medicine Division confidential, but publicize the Radioisotope Program. The very name of the committee had been selected so as not to disclose that 'there might be problems in connection with alleged service-connected disability claims'. George M. Lyon to Committee on Veterans Medical Problems, 8 December 1952, ACHRE Document No. VA-05294-A, as quoted by Advisory Committee, *The Human Radiation Experiments* (n. 21), pp. 300 and 314, footnote 177.

30 Lenoir and Hays, 'Manhattan Project for Biomedicine' (n. 23), p. 54. Lenoir and Hays state that the Atomic Medicine Division was founded in 1947, but, according to the Advisory Committee on Human Radiation Experiments, 'the feared claims from Crossroads did not materialize and … the confidential Atomic Medicine Division was not activated'. Advisory Committee, *The Human Radiation Experiments* (n. 21), p. 300.

31 The VA Hospitals initially involved in the radioisotope program were in Framingham, Massachusetts; the Bronx, New York; Cleveland, Ohio; Hines, Illinois; Minneapolis, Minnesota; and Van Nuys, California. Correspondence between officials at the AEC's Isotope Division and the Veterans Administration about the founding of these Radioisotope Units is in the National Archives, Southeast Region, Manhattan Engineering District/Clinton Engineering Works General Research Correspondence, Acc. No. 67B0803, Box 177, Folder AEC 441.2, R-Veterans Administration.

32 Lenoir and Hays, 'Manhattan Project for Biomedicine' (n. 23), p. 57.

33 Although women physicists were uncommon in the 1940s, there were more in studies of radioactivity. For excellent analysis of the historiography of women in this field of specialization, see Maria Rentetzi, 'Gender, Politics, and Radioactivity Research in Interwar Vienna: The Case of the Institute for Radium Research', *Isis*, **95**, 2004, pp. 359–93. Yalow's biographer offers thoughtful reflection on not only her experiences as a woman scientist, but also as a child and grandchild of Jewish immigrants. As he notes, the New York world of medicine was dominated by Columbia's College of Physicians and Surgeons and Cornell

Medical School, with few Jewish students and almost no Jewish faculty. The Bronx VA Hospital's Department of Medicine appointed a Jewish physician as its chief in 1946, the first of many such appointments. The concentration of Jews, women, and even African-Americans made the department a target of investigation in 1954, as part of the McCarthy era. This was the political and cultural backdrop to Yalow and Berson's early work together, a collaboration of two ambitious, bright Jewish scientists. See Eugene Straus, *Rosalyn Yalow, Nobel Laureate: Her Life and Work in Medicine,* New York: Plenum 1998.

34 One paper based on these experiments was reported to the AEC for the bibliography included in the agency's publication *Isotopes… A Three-Year Summary of US Distribution*, Washington, D.C.: US Government Printing Office, August 1949, p. 89. It was Bernard Roswit, J. Sorrentino, and Rosalyn Yalow, 'The Use of Radioactive Phosphorus (P^{32}) in the Diagnosis of Testicular Tumors', *Journal of Urology,* **63**, 1950, pp.724–8.

35 See Rosalyn S. Yalow, 'Radioactivity in the Service of Humanity', *Interdisciplinary Science Reviews*, **10**, 1985, pp. 56–64 and Straus, *Rosalyn Yalow* (n. 33), pp. 5ff. From 1947 to 1950, Yalow was working as a consultant at the Bronx VA Hospital while teaching at Hunter College; in 1950 she became Assistant Chief of the hospital's Radioisotope Unit.

36 Solomon A. Berson, Rosalyn S. Yalow, Joseph Sorrentino, and Bernard Roswit, 'The Determination of Thyroidal and Renal Plasma I^{131} Clearance Rates as a Routine Diagnostic Test of Thyroid Dysfunction', *Journal of Clinical Investigation*, **31**, 1952, pp. 141–58.

37 Hertz, Roberts, and Evans, 'Radioactive Iodine as an Indicator' (n.14). For more on the early uses of AEC-produced iodine-131, see Creager, 'Nuclear Energy in the Service of Biomedicine' (n. 13).

38 Solomon A. Berson and Rosalyn A. Yalow, 'The Use of K^{42} or P^{32} Labeled Erythrocytes and I^{131} Tagged Human Serum Albumin in Simultaneous Blood Volume Determinations', *Journal of Clinical Investigation*, **31**, 1952, pp. 572–80. For their further studies of blood volume using radioisotopically-labeled red blood cells and serum proteins: Solomon A. Berson, Rosalyn S. Yalow, Abraham Azulay, Sidney Schreiber, and Bernard Roswit, 'The Biological Decay Curve of P^{32} Tagged Erythrocytes. Application to the Study of Acute Changes in Blood Volume', *Journal of Clinical Investigation*, **31**, 1952, pp. 581–91; Solomon A. Berson, Rosalyn S. Yalow, Sidney S. Schreiber, and Joseph Post, 'Tracer Experiments with I^{131} Labeled Human Serum Albumin: Distribution and Degradation Studies', *Journal of Clinical Investigation*, **32**, 1953, pp. 746–68; Solomon A. Berson and Rosalyn S. Yalow, 'The Distribution of I^{131} Labeled Human Serum Albumin Introduced into Ascitic Fluid: Analysis of the Kinetics of a Three Compartment Catenary Transfer System in Man and Speculations on Possible Sites of Degradation', *Journal of Clinical Investigation*, **33**, 1954, pp. 377–87.

39 The first guidelines that legally distinguished between human treatment and experiment date to Germany, 1931. The difference between therapeutic and non-therapeutic experiments became central to post-war medical ethics as codified in the Nuremberg Code and the Declaration of Helsinki. See Jordan Goodman, Anthony McElligott, and Lara Marks, 'Making Human Bodies Useful: Historicizing Medical Experiments in the Twentieth Century', in Goodman, McElligott and Marks (eds), *Useful Bodies* (n. 12), pp. 1–23, at p. 9.

40 The expert was Dr I. Arthur Mirsky, who put forth this theory in 1952 about adult-onset diabetes in his lectures at the Laurentian Hormone Conference, published as 'The Etiology of Diabetes Mellitus in Man', *Recent Progress in Hormone Research*, **7**, 1952, pp. 437–67. His theory of rapid degradation took into account that 'the pancreata of adult diabetics contained almost normal amounts of insulin' (Yalow, 'Radioactivity' (n. 35), p. 58).

41 Solomon A. Berson, Rosalyn S. Yalow, Arthur Bauman, Marcus A. Rothschild, and Katharina Newerly, 'Insulin-I^{131} Metabolism in Human Subjects: Demonstration of Insulin Binding Globulin in the Circulation of Insulin Treated Subjects', *Journal of Clinical Investigation*, **35**, 1956, pp. 170–90.

42 See F.E. James, 'Insulin Treatment in Psychiatry', *History of Psychiatry*, **3**, 1992, pp. 221–35.

43 See Rosalyn S. Yalow, 'Development and Proliferation of Radioimmunoassay Technology', *Journal of Chemical Education*, **76**, 1999, pp. 767–68.

44 Yalow states that the concept that small peptides could elicit plasma antibodies 'was not acceptable to immunologists until the 1950s'. Rosalyn S. Yalow, 'Radioimmunoassay: A Probe for the Fine Structure of Biologic Systems', *Science*, **200**, 1978, pp. 1236–45, at p. 1237. In the 1945 edition of his book, Karl Landsteiner gives a sense of the uncertainty as to whether serum proteins that neutralize hormones should be called antibodies or not. He states that insulin has an antigenic capacity but that it is low 'fortunately for therapeutic use'. The passage continues: 'After continued administration of various hormones neutralizing agents can appear in the serum for which the term "anti-hormones" has been adopted. … The moot question in this line of research – supposing the mechanism is always the same – is whether the neutralizing substances found in the serum are antibodies in the serological sense or, according to Collip's theory, antagonistic hormones present in small amounts also in normal animals . . . In favor of the antibody theory is the fact that neutralizing sera have not been reliably demonstrated against low-molecular hormones, e.g. adrenalin or estrin . . .' (Karl Landsteiner, *The Specificity of Serological Reactions*, revised edition, Cambridge, MA: Harvard University Press, 1945, p. 37).

45 Straus, *Rosalyn Yalow* (n. 33), p. 8.

46 Yalow, 'Radioimmunoassay: A Probe' (n. 44), p. 1238.

47 Berson, Yalow, Bauman, Rothschild, and Newerly, 'Insulin-I^{131} Metabolism in Human Subjects' (n. 41).

48 See Advisory Committee, *Human Radiation Experiments* (n. 21), p. 186.

49 Rosalyn S. Yalow and Solomon A. Berson, 'Assay of Plasma Insulin in Human Subjects by Immunological Methods', *Nature*, **184**, 1959, pp. 1648–9; Rosalyn S. Yalow and Solomon A. Berson, 'Immunoassay of Endogenous Plasma Insulin in Man', *Journal of Clinical Investigation*, **39**, 1960, pp. 1157–75; Rosalyn S. Yalow and Solomon A. Berson, 'Immunoassay of Plasma Insulin in Man', *Diabetes*, **10**, 1960, pp. 339. Their method used as reagents ^{131}I-labeled insulin and antibodies isolated from guinea pigs immunized with crystalline beef insulin.

50 The serum levels of insulin measured using RIA were significantly lower than levels of insulin-like bioactivity determined using other methods; this discrepancy led to a fifteen-year controversy over the forms and level of insulin activity. See C. Ronald Kahn and Jesse Roth, 'Berson, Yalow, and the *JCI*: The Agony and the Ecstasy', *Journal of Clinical Investigation*, **114**, 2004, pp. 1051–4.

51 Roger P. Ekins, 'The Estimation of Thyroxine in Human Plasma by an Electrophoretic Technique', *Clinica Chimica Acta*, **5**, 1960, pp. 453–9; Roger P. Ekins, 'Immunoassay, DNA Analysis, and Other Ligand Binding Assay Techniques: From Electropherograms to Multiplexed, Ultrasensitive Microarrays on a Chip', *Journal of Chemical Education*, **76**, 1999, pp. 769–80.

52 On the medical uses of radioisotopes associated with Great Britain's atomic energy program, see Alison Kraft, 'Between Medicine and Industry: Medical Physics and the Rise of the Radioisotope 1945–65', *Contemporary British History*, **20**, 2006, pp. 1–35.

53 R.H. Unger, A.M. Eisentraut, M.S. McCall, S. Keller, H.C. Lanz, and L.L. Madison, 'Glucagon Antibodies and Their Use for Immunoassay for Glucagon', *Proceedings of the Society for Experimental Biology and Medicine*, **102**, 1959, pp. 621–3.

54 For an account of postwar endocrinology that attends to other significant applications of radioisotopes, see Philippe Fragu, 'How the Field of Thyroid Endocrinology Developed in France after World War II', *Bulletin for the History of Medicine*, **77**, 2003, pp. 393–414.

55 S.M. Glick, J. Roth, R.S. Yalow, and S.A. Berson, 'Immunoassay of Human Growth Hormone in Plasma', *Nature*, **199**, 1963, pp. 784–7; J. Roth, S.M. Glick, R.S. Yalow, and S.A. Berson, 'Hypoglycemia: A Potent Stimulus to Secretion of Growth Hormone', *Science*, **140**, 1963, pp. 987–8; S.A. Berson and R.S. Yalow, 'Radioimmunoassay of ACTH in Plasma', *Journal of Clinical Investigation*, **47**, 1968, pp. 2725–51; R.S. Yalow, S.M. Glick, J. Roth, and S.A. Berson, 'Radioimmunoassay of Human Plasma ACTH', *Journal of Clinical Endocrinology and Metabolism*, **24**, 1964, pp. 1219–25; Solomon A. Berson, Roslyn S. Yalow, G.D. Aurbach, and John T. Potts, Jr., 'Immunoassay of Bovine and Human Parathyroid Hormone', *Proceedings of the National Academy of Sciences USA*, **49**, 1963, pp. 613–17; R.S. Yalow and S.A. Berson, 'Radioimmunoassay of Gastrin', *Gastroenterology*, **58**, 1970, pp. 1–14.

56 See Andrzej Bartke, 'The Early Days of Steroid Radioimmunoassays at the Worcester Foundation', *Endocrinology*, **129**, 1991, pp. 2277–8.

57 A mole is a unit of measurement corresponding to the amount of a substance that contains as many molecules or elementary units as the number of atoms in 0.012 kilogram of carbon 12. The number is 6.023×10^{23}.

58 See Yalow, 'Radioimmunoassay: A Probe' (n. 44), pp. 1239–40.

59 Straus, *Rosalyn Yalow* (n. 33), p. 13.

60 John C. Charlton, 'Overcoming the Radiological and Legislative Obstacles in Radioimmunoassay', in H. Schönfeld (ed.), *New Developments in Immunoassays*, *Antibiotics & Chemotherapy*, vol. 26, Basel: S. Karger, 1979, pp. 27–37. Radioimmunoassays can be performed with other radiolabels, such as carbon-14 or tritium, but iodination is often the easiest way to introduce the label, and the gamma radiation emitted by iodine-131 and iodine-125 is easy to detect.

61 For an account of the establishment and growth of New England Nuclear, see Angela N.H. Creager, 'The Industrialization of Radioisotopes by the US Atomic Energy Commission', in Karl Grandin, Nina Wormbs, and Sven Widmalm (eds), *The Science-Industry Nexus: History, Policy, Implications*, Proceedings of Nobel Symposium 123, Sagamore Beach, MA: Science History Publications, 2004, pp. 143–67.

62 Copy of New England Nuclear 1973 Annual Report, courtesy of Paul McNulty.

63 Yalow, 'Radioimmunoassay: A Probe' (n. 44), p. 1245. Yalow and Berson developed the radioimmunoassay for hepatitis-associated antigen: J.H. Walsh, R.S. Yalow, and S.A. Berson, 'Radioimmunoassay of Australia Antigen', *Vox Sanguinis*, **19**, 1970, pp. 217–24; J.H. Walsh, R.S. Yalow, and S.A. Berson, 'Detection of Australia Antigen and Antibody by Means of Radioimmunoassay Techniques', *Journal of Infectious Diseases*, **121**, 1970, pp. 550–4.

64 Elliott Block, 'An Overview of Radioimmunoassay Testing and a Look at the Future', in Schönfeld (ed.), *New Developments in Immunoassays* (n. 60), pp. 1–9, at pp. 3–4.

65 Ronald B. Herberman, 'Immunodiagnostics for Cancer Testing', in Schönfeld (ed.), *New Developments in Immunoassays* (n. 60), pp. 38–44; Rosalyn S. Yalow, 'Radioimmunoassay in Oncology', *Cancer*, **53**, 1984, pp. 1426–31.

66 Block, 'Overview of Radioimmunoassay Testing' (n. 64), p. 2. Carcino-embryonic antigen goes by the acronym CEA.

67 John Landon, 'A Look at the Future with Regard to Immunoassay', in Schönfeld (ed.) *New Developments in Immunoassays* (n. 60), pp. 118–28.

68 Paul A. Brown, 'A Large Private Laboratory Looks at Immunoassay', Schönfeld (ed.), *New Developments in Immunoassays* (n. 60), pp. 98–104.

69 Of the six instrument systems available in 1979, three were designed for discrete sample processing (by Union Carbide, Micromedic, and Bagshawe-Kemble) and three for continuous flow (by Schwarz-Mann/Becton Dickinson, Technicon, and Squibb). Stanley J. Goldsmith, 'Trends and Developments in Radioimmunoassay Instrumentation', Schönfeld (ed.) *New Developments in Immunoassays* (n. 60) pp. 45–60.

70 One publication from the 1970s cites reliance on animal sera as a component as one of the technical difficulties facing investigators using RIA: Vincent Marks, 'New Developments in Immunoassays for Therapeutic Drug Monitoring', Schönfeld (ed.) *New Developments in Immunoassays* (n. 60) pp. 16–26.

71 Ekins, 'Immunoassay' (n. 51), p. 770. The development of hybridoma technology received heightened publicity in 1984, when Köhler and Milstein received the Nobel Prize in Physiology or Medicine for this advance.

72 Cambrosio and Keating, *Exquisite Specificity* (n. 1), especially chapter 2. The authors detail the various ways that key 'tacit knowledge' was transmitted between laboratories.

73 Arthur Klausner, 'Immunoassays Flourish in New Markets', *Bio/technology*, **5**, 1987, pp. 551–6.

74 Assays using non-isotopic labels often rely on having the antibody linked to a particular enzyme; the chromogenic version uses as its indicator molecule a colorless substrate that is converted into a visible product by the enzyme. The concentration of the antigen of interest is directly proportional to the intensity of color measured.

75 Block, 'Overview of Radioimmunoassay Testing' (n. 64), p. 9.

76 Rebecca Krumm, 'Radioimmunoassay: A Proven Performer in the Bio Lab', *The Scientist*, **8**, 1994, pp. 16–17.

77 Ibid., pp. 16–17.

78 Ibid.

79 Jacques Normand, Richard O. Lempert, and Charles P. O'Brien (eds), *Under the Influence?: Drugs and the American Work Force*, Washington, D.C.: National Academy Press, 1994, p. 179.

80 Ibid., pp. 180–5.

81 For example, the US Air Force uses RIA to test for LSD, which is not on NIDA's drug panel. See the webpage on 'The Airforce Urinalysis Program', published by Hanscom Air Force Base <http://www.hanscom.af.mil/abw-ja/1ST%20SERGEANT-C/urinalysis_program.aspx> accessed 13 July 2006.

82 J.P. Sherry, 'Environmental Chemistry: The Immunoassay Option', *Critical Reviews in Analytical Chemistry*, **23**, 1992, pp. 217–300; R.O. Harrison and G.H. Eduljee, 'Immunochemical Analysis for Dioxins – Progress and Prospects', *Science of the Total Environment*, **239**, 1999, pp. 1–18.

83 Klausner, 'Immunoassays Flourish' (n. 73), p. 555.

84 See Ingrid Wengatz, Adam S. Harris, S. Douglass Gilman *et al.*, 'Recent Developments in Immunoassays and Related Methods for the Detection of Xenobiotics', in Jeanette M. Van Emon, Clare L. Gerlach, and Jeffre C. Johnson (eds), *Environmental Immunochemical*

Methods: Perspectives and Applications,Washington, D.C.: American Chemical Society, 1996, pp. 110–26.

85 M.T. Meyer, J.E. Bumgarner, Jerry L. Varnes, J.V. Daughtridge, E.M. Thurman, and Kenneth A. Hostetler, 'Use of Radioimmunoassay as a Screen for Antibiotics in Confined Animal Feeding Operations and Confirmation by Liquid Chromatography/Mass Spectrometry', *The Science of the Total Environment*, **248**, 2000, pp. 181–7.

86 Wengatz *et al.*, 'Recent Developments in Immunoassays' (n. 84), p. 111.

87 Klausner, 'Immunoassays Flourish' (n. 73), p. 555.

88 On resistance to mandatory drug testing, see Normand, Lempert, and O'Brien, *Under the Influence?* (n. 79), p. 182.

89 See Angela N.H. Creager, 'Tracing the Politics of Changing Postwar Research Practices: The Export of 'American' Radioisotopes to European Biologists', *Studies in History and Philosophy of the Biological and Biomedical Sciences*, **33**, 2002, pp. 367–88; Creager, 'Nuclear Energy in the Service of Biomedicine' (n. 13); and Creager, 'The Industrialization of Radioisotopes' (n. 61).

90 See Stephen Bocking, 'Ecosystems, Ecologists, and the Atom: Environmental Research at Oak Ridge National Laboratory', *Journal of the History of Biology*, **28**, 1995, pp. 1–47 and idem, *Ecologists and Environmental Politics: A History of Contemporary Ecology*, New Haven: Yale University Press, 1997.

91 E.F. Pfeiffer, 'Impact of Insulin Research upon Biomedicine and Clinical Investigation', *Hormone and Metabolic Research, Supplement Series*, **26** (suppl.), 1992, pp. 1–12. For information on this author, see K. Federlin and S. Raptis, 'Ernst F. Pfeiffer: His Impact on Diabetes Research and Treatment Over the Last 45 Years', *Experimental and Clinical Endocrinology & Diabetes*, **109** (suppl. 2), 2001, pp. S83–5.

92 For an insightful treatment of the historiography on clinical innovation (and related concerns in sociology and anthropology of medicine) see the introductory chapter of Ilana Löwy, *Between Bench and Bedside: Science, Healing, and Interleukin-2 in a Cancer Ward*, Cambridge, MA: Harvard University Press, 1996.

93 On the longer history of human experimentation: Susan E. Lederer, *Subjected to Science: Human Experimentation in America Before the Second World War*, Baltimore, MD: Johns Hopkins University Press, 1995; Goodman, McElligott and Marks (eds), *Useful Bodies* (n. 12).

94 This series of articles, for which the journalist received a 1994 Pulitzer Prize, was published in the *Albuquerque Tribune*. She went on to publish a book on the subject: Eileen Welsome, *The Plutonium Files: America's Secret Medical Experiments in the Cold War*, New York: Random House, 1999.

95 'US Admits to Concealing Human Radiation Experiments', 8 December 1993, document in DOE/NV Nuclear Testing Archive, Las Vegas, NV, as reference in the Department of Energy's OpenNet Database <http://www.osti.gov/opennet/> accessed 11 June 2004.

96 Advisory Committee, *Human Radiation Experiments* (n. 21).

97 Ibid., p. 175.

98 Ibid., pp. 46–7, 173, 189.

99 Ibid., pp. 185–6.

100 Barton C. Hacker, *The Dragon's Tail: Radiation Safety in the Manhattan Project, 1942–1946*, Berkeley, CA: University of California Press, 1987; Claudia Clark, *Radium Girls: Women and Industrial Health Reform, 1910–1935*, Chapel Hill, NC: University of North Carolina Press, 1997.

101 J. Samuel Walker, *Permissible Dose: A History of Radiation Protection in the Twentieth Century*, Berkeley, CA: University of California Press, 2000, chapter 1.

102 Advisory Committee, *Human Radiation Experiments* (n. 21), p. 213.

103 Ibid., p. 214.

104 For more on this case and the role of historians on both sides, see David J. Rothman, 'Serving Clio and Client: The Historian as Expert Witness', *Bulletin of the History of Medicine*, **77**, 2003, 25–44.

105 Advisory Committee, *Human Radiation Experiments* (n. 21), p. 196 (the entirety of chapter 7 is devoted to 'Nontherapeutic Research on Children').

106 Ibid., especially pp. 212–13.

107 Ibid., chapter 10, 'Atomic Veterans'. Not all of the radiation exposure was intentional on the part of the military, and there was little attention (or scientific understanding) of the long-term effects of low-level radiation.

108 Ibid., pp. 283–4

109 Weisgall, *Operation Crossroads* (n. 27), p. 278.

110 E.g., Yalow, 'Radioimmunoassay: A Probe' (n. 44), and Rosalyn S. Yalow, 'Radioimmunoassay: Its Relevance to Clinical Medicine', in S. Philip Bralow and Rosalyn S. Yalow (eds), *Basic Research and Clinical Medicine*, Washington, D.C.: Hemisphere Publishing, 1981, pp. 3–22.

CHAPTER ELEVEN

Emerging Paradigm, Emerging Disease: Molecular Immunology and AIDS in the 1980s

Victoria A. Harden

During the quarter century since AIDS was recognized in 1981, scholars and popular writers have produced a great outpouring of literature about many aspects of this disease. This paper will focus on a narrow but critically important segment of AIDS history that has not been explored as thoroughly as the social and political contexts. It will examine aspects of the intellectual context within which scientists at the US National Institutes of Health (NIH) thought about this disease from their earliest encounter with an AIDS patient in 1981 until the human immunodeficiency virus was demonstrated as the cause of AIDS in 1984.[1] Based on this case study, I will argue that the intellectual paradigm of molecular immunology, within which early AIDS research was conducted at the NIH, was incomplete in the early 1980s, and that investigators utilized their partial knowledge to combat AIDS while simultaneously working to expand the intellectual scaffolding within which they could formulate new interventions.

Beginning about mid-1980, physicians began to see two anomalous medical problems. First were young men with what were called 'opportunistic infections'. These infections were caused by microbes that usually were kept in check by the human immune system and that flared up only when they had the opportunity provided by an extraordinary shutdown of the immune system, such as that caused by radiation to prevent rejection of transplanted bone marrow. The other strange medical phenomenon was Kaposi's sarcoma, a skin cancer usually seen only in elderly men with a Mediterranean background. Now it was occurring in seemingly healthy younger men. Physicians are trained with the mnemonic, 'When you hear hoof beats, think first of horses, not zebras'. Thus physicians must have put down the first few AIDS cases as just something they personally did not recognize. As time went on, however, and similar cases were seen and mentioned to colleagues in telephone calls and at medical meetings, it gradually dawned on physicians that maybe these phenomena represented something new, a 'zebra' disease, a disease not previously encountered. On June 5, 1981, Michael Gottleib at the University of California, Los Angeles, and his colleagues published the first medical article about AIDS in the United States. It was a short article about the opportunistic pneumonia caused by *Pneumocystis carinii* (PCP), and it appeared in the Centers for Disease Control's weekly journal, *Morbidity and Mortality Weekly Report*, or *MMWR*. In the 'Editorial Note' following the case descriptions, the authors ventured no more than this cautious statement: 'All of the above observations suggest the possibility

of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis'.[2]

A month later, the *MMWR* published a second report from Alvin Friedman-Kein at New York University Medical Center and a large number of his colleagues in New York and California hospitals, noting that Kaposi's sarcoma was also being observed in men in the gay communities on both coasts. A link to the Gottleib paper was made via the observation that some of the patients with Kaposi's sarcoma also suffered from PCP and other opportunistic infections. Both papers observed that the population in which the symptoms were found was homosexual males.[3] By the end of August 1981, a third paper was published in *MMWR*, this one submitted by public health officials at the local, state, and federal level. It contained epidemiological tables related to incidence of the diseases, noted that laboratory studies on possible suppression of the immune system were underway, that active disease surveillance was in progress, and a national case-control study planned. This paper sent a strong signal indicating that the medical community had been persuaded by the number of similar cases and patterns of disease in defined populations that a new disease was not just possible, but apparently probable.[4]

How was the US federal government structured to respond to a new infectious disease? Figure 11.1 shows the public health agencies of the US Department of Health and Human Services (DHHS). Three agencies – the NIH, the Centers for Disease Control (CDC), and the Food and Drug Administration (FDA) – were technically

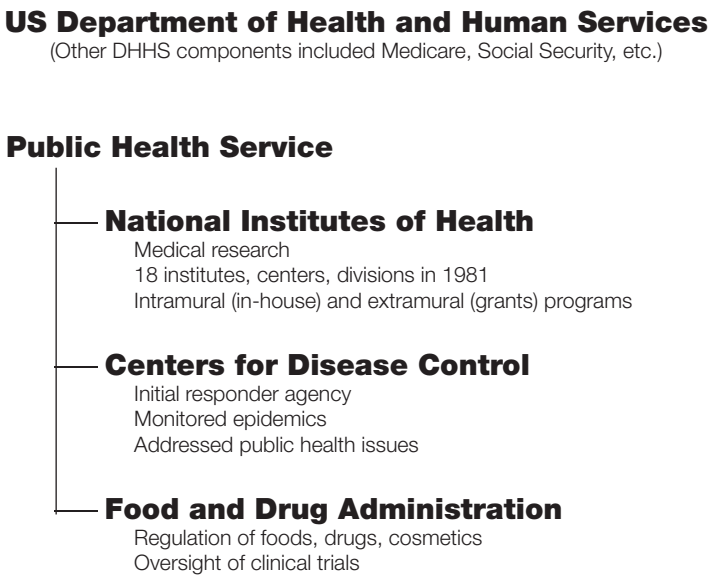

Figure 11.1 Organizational chart of the public health components of the US Department of Health and Human Services, 1981. Source: Office of NIH History, National Institutes of Health.

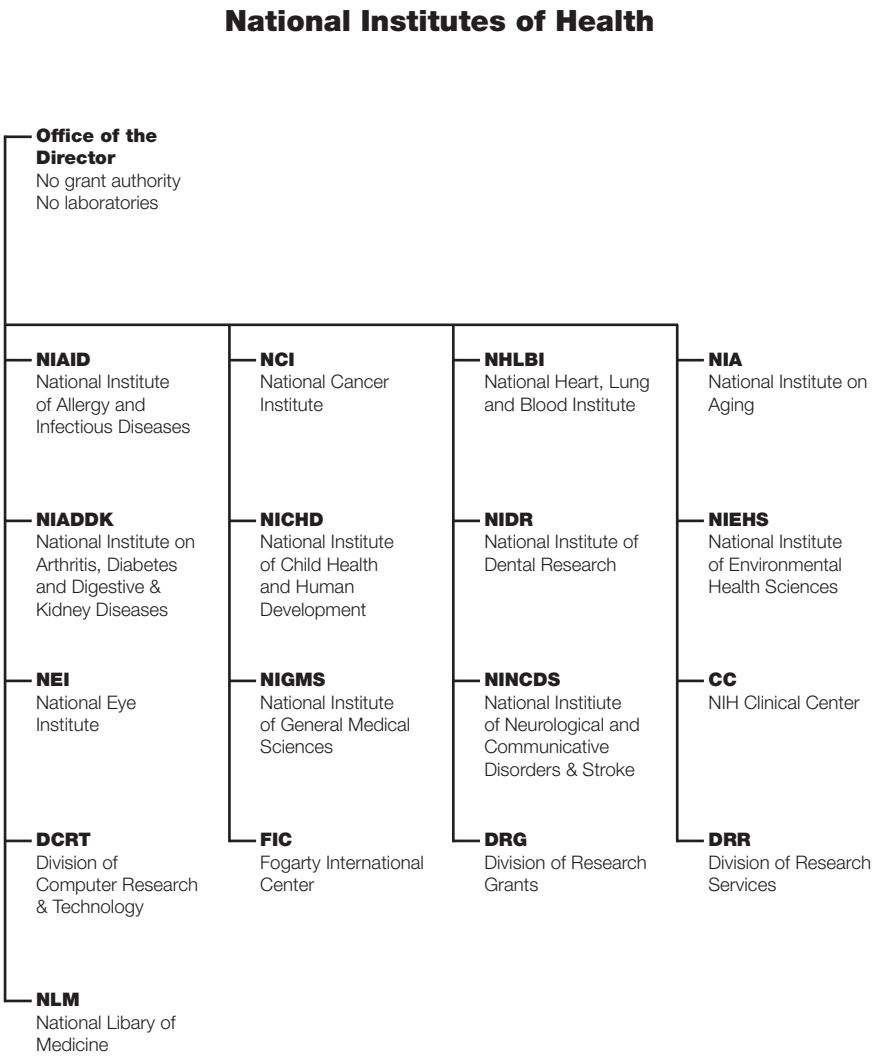

Figure 11.2. Organizational Structure of the National Institutes of Health, 1981. Source: Office of NIH History, National Institutes of Health.

subsumed under the US Public Health Service (PHS), but, in fact, in 1981 the PHS primarily supervised the personnel of the Commissioned Officers Corps, not the civil servants who also worked in the agencies. The directors of the NIH, the CDC, and the FDA all reported to the DHHS Assistant Secretary for Health, not to the PHS Surgeon General.[5] As they had evolved historically, moreover, the three agencies had specialized missions: the NIH conducted medical research; the CDC responded to epidemic outbreaks, such as Legionnaire's disease in 1976 and toxic shock syndrome in 1980; and the FDA regulated food, drugs, and cosmetics. In 1981, the boundary lines between these agencies were clear. The advent of AIDS introduced a strain into this system that has been discussed by many authors, especially related to questions of the speed of making promising AIDS treatments available, access to and conduct of clinical trials, and coordination among agencies.[6]

The agency charged with research on understanding diseases was the National Institutes of Health. Figure 11.2 shows the eighteen components of the NIH in 1981. By 2006, the number of components had increased to twenty-seven. Most of the Institutes, Centers, and Divisions shown in this figure had been created since World War II by a combination of forces including disease lobby groups such as the American Cancer Society and their Congressional backers, who liked to vote for health. With respect to a new disease whose first symptoms included pneumonia and a rare cancer, both the National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute (NCI) might well have argued that they should claim 'lead institute' status with respect to AIDS. Later, when AIDS was shown to be transmissible by blood, the National Heart, Lung, and Blood Institute might also have claimed a major stake in AIDS research. As other organs were identified as having AIDS involvement, the National Eye Institute, the National Institute of Dental Research, the National Institute of Neurological and Communicative Disorders and Stroke, and most of the other components were also drawn into research on AIDS. Because of the historical growth of the NIH, however, AIDS did not fit neatly into any single category in the existing structure, and it took some time and some friction to work out internal coordination and the divisions of responsibility.[7]

The NIH is divided into an extramural or grants program, originally launched in 1946, to which 80 per cent of the NIH budget is dedicated, and an intramural programme, in the NIH's own laboratories, which receives about 11 per cent of the budget. Both of these funding mechanisms were involved with research on AIDS, although the grants program was slower because of its administrative structure. The process for making awards is two tiered. First, a panel of experts in the field of any proposal – the peers of the requesting scientist – evaluate the proposal for scientific merit and award a score. After this peer review, the proposal is sent to an institute's advisory council, which includes lay members, and which can change the weight given to proposals if they believe particular areas of research should be promoted. In 1981, the time from an investigator's submission of a proposal to the time funds were received was about eight or nine months, under normal circumstances. In the 1980s, many writers were outraged that the NIH grants process was so slow to get new money to AIDS researchers in universities. The speed of the process, however, had never been of concern before the advent of AIDS.[8]

Because of this slow-moving process in the earliest years of AIDS, much early research on AIDS occurred in the NIH intramural programme, whose flexibility permitted a rapid shift of resources to the new disease. The NIH intramural programme is comprised of a series of laboratories, primarily in Bethesda, Maryland, in which the scientific staff are civil servants, members of the PHS Commissioned Corps, or trainees in various programmes. Between 1953 and 1990, one group of trainees was called Clinical Associates. They were young physicians who could satisfy their military obligation with two years' research at NIH. During the Vietnam War, these self-styled 'Yellow Berets' were chosen in a highly competitive climate. They received rigorous training in clinical research while at the NIH, and many of them transplanted these methods to the medical schools around the country where they pursued their careers. Some of the Clinical Associates stayed in the intramural programme at NIH, however, and among them were the three leaders of intramural AIDS research in the 1980s, Anthony Fauci, Robert Gallo, and Samuel Broder.[9] Within the NIH intramural programme, the chief of a laboratory or branch could redirect the research program overnight if he so wished. This was because funding was stable, and not dependent on grants. The work of the laboratory was reviewed usually every three years by a non-NIH group of scientists called the Board of Scientific Counselors for each institute. So long as a laboratory's work was endorsed by this group, the scientists could pursue their own interests. [10]

Before examining the specific activities in the NIH intramural program's response to AIDS, the intellectual context with respect to immunology in which scientists formulated their research needs to be explored. Scientists can only devise responses to any disease within the mental construct they have of how the human body works. When the earliest responders to AIDS recognized that it did not fit existing disease descriptions, they initially defined it according to its symptoms and common immune-deficiency characteristic. Once the scientific community recognized AIDS as a new disease entity, the concept of its pathology was developed within an intellectual paradigm that allowed scientists to think about disease at the molecular level.

The march of discovery at the cutting edge of research in what became molecular immunology began in the mid-1950s, when new discoveries in immunology moved the theoretical and experimental interests of chemical and biological immunologists closer to one another. In 1956, the antibody-producing cells were defined as 'B cells' because they were shown to be produced in the bone marrow. In 1961, other immune-system cells derived from the thymus gland and called 'T cells' were shown to be important in a different kind of immunological reaction called 'cell-mediated immunity'. In 1975 recombinant DNA techniques made it possible to produce monoclonal antibodies – antibodies produced by a single line of cells and that recognized a single narrowly-defined epitope or receptor. In 1976 an assay was developed to detect and measure antibody production by human lymphocytes at the single-cell level. In 1981, the structure of a major histocompatibility complex antigen was completed.[11] One scientist recalled the excitement in the early 1960s:

> In a very wonderful meeting in Sanibel Island, Florida, in about 1963, scientists first began to talk about these diseases in terms of the type of cell and the immune function involved. The tests for T-cell functions emerged from various laboratories.... The next phase first involved the use of heteroantibodies, then of hybridoma technology and monoclonal

> antibodies, to define differences in the surface of T cells with different functions. CD4 and CD8 antibodies were defined. CD4, the entry site for HIV, was not known until the late 1970s when Dr. [Pat] Kung of Ortho Scientific, in conjunction with Drs. [Ellis] Reinherz and [Stewart] Schlossman of Harvard and many others, contributed by making monoclonal antibodies to this protein.[12]

This exciting new knowledge, however, emerged piecemeal as a new intellectual structure, and it was not rapidly incorporated into ordinary clinical practice. In the preface to E.J. Holborow and W.G Reeves's 1979 textbook of immunology, for example, the editors noted, 'The large majority of doctors in practice today escaped any specific training in immunology and many find its unfamiliar jargon and growing complexity formidable'.[13] Even in 1983, a publication entitled 'Understanding the Immune System', which was prepared to help physicians understand the new discoveries in immunology, reflected the inconclusive nature of many of the findings. It stated that it was 'becoming increasingly clear' – note that it did not say, 'it is clear' – that the two arms of the immune system were closely related.[14]

One characteristic of the emerging nature of the theoretical scaffolding in 1980 was the lack of consistency in terminology. The term 'lymphokine', for example, had been introduced in 1969, but in 1980, the following synonyms were still in use for it: lymphocyte mediator, soluble lymphocyte mediator, lymphocyte activation product, soluble lymphocyte product (or factor), mediator (or soluble mediator) of cellular (or cell-mediated) immunity, soluble mediator of immunologic regulation.[15] The methods for studying cells of the immune system were also labor intensive, as a number of investigative technologies either did not yet exist or were not widely available in practice. Although flow cytometry had been developed by the early 1970s and a fluorescence-activated cell sorter, or FACS machine, had been introduced commercially in 1975, the

Theoretical Scaffolding for Studying Infectious Diseases, 1900, 1981

Germ theory of infectious diseases, 1900	Molecular immunology, 1981
Vectors known: insect, water, milk, healthy human carrier	B cells, T cells known
Limited number of therapies and vaccines	Lymphokines known
All types of microorganisms not identified	Receptor concept known
Relationships among microbes and vectors not fully understood	Chemokines not known independently
	How to identify any given receptor not known

Figure 11.3 Theoretical scaffolding for studying infectious diseases, 1900, 1981. Source: Victoria A. Harden, 'The Scientific Construction of New Diseases: Rocky Mountain Spotted Fever and AIDS as Comparative Case Studies', in Martha L. Hildreth and Bruce T. Moran (eds) *Disease and Medical Care in the Mountain West: Essays on Region, History, and Practice*, Reno: University of Nevada Press, 1998, pp. 59–71.

first publications in which it was used to study B and T cells in AIDS cases were in 1983 and 1984, according to a search of the US National Library of Medicine's database.[16] At the NIH, as we will see, one institute had purchased a FACS machine for use in AIDS research by late 1981, but another did not have the instrument available. The polymerase chain reaction, or PCR, was another technique now commonplace in molecular biology that was not developed until the mid-1980s and not cited in AIDS publications until 1988.[17] Computer analysis of data about immunological cells, moreover, was done in the early 1980s on computers such as the PDP-11, whose memory cache was small and which had no large storage mechanism.[18] Computer programmes to analyze the data and produce sophisticated curves did not yet exist. In one of the first texts in 1980 to discuss analysis of lymphocytes by flow cytometry, the author suggested that an entire computer be dedicated to the task because of its complexity: 'A machine with at least 64 K core memory is highly desirable', they wrote. 'A disc with 10 megawords is the very minimum'.[19]

Figure 11.3 compares the understanding of molecular immunology when AIDS made its advent in 1981 to the understanding of the germ theory in 1900, when diseases caused by rickettsial, bacterial, viral, and other microscopic organisms were challenging investigators. At each point in time, the basic structure of a new intellectual system was known, but much detail remained to be understood. With respect to molecular immunology's parent discipline, molecular biology, accretions of knowledge had been incremental and steady within the biomedical research community since the 1940s. Yet the tools for utilizing this knowledge, such as flow cytometry, had not become standard among clinical investigators in the years before the advent of AIDS, let alone among practicing clinicians. The power of the new concept of molecular immunology – its promise for understanding disease on a molecular level – was irresistible to scientists trained in the 1970s, however, and the phenomenon was international in scope. Scientists all over the world agreed that the symptoms they saw in early AIDS cases suggested an underlying immune deficiency.[20]

The magnitude of the generational difference in thinking about infectious diseases between immunologists trained before and after the shift to molecular understanding may be seen in the responses of two NIAID directors to the question, 'What would have happened if AIDS had struck in 1955?' Richard Krause, NIAID director from 1975–84, was trained in the pre-molecular biology era. He responded that 'The principles for identifying sexual transmission of a disease were in place ... We would have used cruder immunologic techniques to make a diagnosis ... A 1950s serological diagnostic test would have been somewhat more primitive, but I think we would have come up with something'. Anthony Fauci, in contrast, who has been NIAID director since 1984, matured as an investigator within the intellectual climate of molecular medicine. His response emphasized how much molecular thinking had made older models of disease control seem helpless: 'I think we would not have had a clue as to how to come at this disease from a basic scientific standpoint. I think we would have realized just on epidemiological grounds that it was an infectious agent of some sort that was sexually transmitted and transmitted by blood. But about pathogenic mechanisms, we wouldn't have had a clue'.[21]

With molecular immunology as an intellectual framework, much of the earliest research on AIDS was conducted at the NIH from 1981 to 1984, before an aetiological

agent was identified. AIDS came to the NIH Clinical Center, the research hospital on the Bethesda campus, on 16 June 1981. The first patient was a young homosexual man beset by severe opportunistic infections who had essentially no immune response. He was admitted to the Omnibus Metabolism Branch protocol of Thomas Waldmann, a distinguished senior immunologist who had been the first to demonstrate the existence of suppressor T cells. Waldmann was head of the Metabolism Branch in NCI. His group was working to define what made the immune system work normally and what the clinical consequences were of abnormal functioning. As part of these studies, he had seen hundreds of patients with different forms of immunodeficiency disease. Waldmann hoped to learn something from this patient in 1981 who apparently had a profound immune deficiency that was different from the genetic Severe Combined Immune Deficiency that was known in children. Waldmann described the first patient in these words:

> The patient, unknown to his family, to us, or to the referring physicians, was a thirty-five year old homosexual man who had been living in New York. He had a particular partner but many other partners as well within the gay community. He had been healthy with the exception of an array of venereal diseases, including syphilis and gonorrhea on a number of occasions, but then he began having lassitude and weakness in February 1981. Weight loss and fever ensued, and he was admitted in April 1981 to the Hartford Hospital where he had *Pneumocystis carinii* pneumonia, lymphocytopenia, cytomegalovirus [CMV] in the blood and urine, herpes simplex II perianaly, *Candida* oesophagitis, and *Mycobacterium avium* tuberculosis of the lung, bone marrow, and esophagus. Initially, he was not as ill as you might have suspected from this history ... We looked at the ability of the patient's cells to make immunoglobulin molecules *in vitro* in a culture system we had developed in 1974 ... This patient could not make immunoglobulins with his cells in tissue culture. These cells in co-culture with my cells inhibited my cells' capacity to make immunoglobulin. Others in the branch studied his cell-mediated immunity. He was unable to make a skin test response to tuberculin, despite the fact that he had widespread *Mycobacterium avium*, nor could he respond to diphtheria and tetanus antigens to which he had been immunized and to which all the rest of us were responsive. These were the *in vivo* evidences in this person of a cellular defect ... The lymphocyte count was profoundly low in the patient, below 1,000 cells per cubic millimeter ...[22]

By 28 October, despite heroic efforts to combat the multiple pathologies, the patient died. When AIDS was eventually identified as an infectious disease, Waldmann and his laboratory turned back to their ongoing research on the immunology of cancer.[23]

Another center for immunological research at the NCI was the group of young researchers who were interested in the relationship between the immune system and cancer and who wanted to use epidemiological methods to track so-called outbreaks of cancer. James Goedert and William Blattner were two of these young physicians. Blattner had taken evening courses at NIH in immunology, and in the first few months of 1981 collaborated with another colleague, James Goedert, on an unusual case of Kaposi's sarcoma in New York. Goedert noted that the young man, the brother of a friend of one of his family members, had two lesions that were reportedly diagnosed as Kaposi's sarcoma. 'They must be wrong. That is impossible', Goedert told him. 'In my whole career, [I had] seen one case in an elderly Jewish man whose general practitioner had said, "I think this is Kaposi's sarcoma"'. Goedert took slides of the young man's lesions

to the Armed Forces Institute of Pathology at Walter Reed Army Institute of Research. 'The eminent pathologists at AFIP in the Sarcoma Section said, "No, this is not Kaposi's sarcoma, this is angiosarcoma"'. But Goedert's patient's sister had discovered that more young men in New York were exhibiting KS lesions and put Goedert in touch with their physician. He confirmed six cases of KS and noted that 'they are all gay'. 'Is your patient gay?' he asked. Goedert replied that he did not know. 'Times have changed in terms of what we ask our patients', Goedert stated. 'In the end my patient reluctantly acknowledged that he was gay. That was a time, especially for a young professional, when it was not something that was out in the open'.[24]

In 1981, NCI had considerably more money available than other NIH institutes because of its unique status under the 1971 National Cancer Act in the so-called 'War on Cancer'. Blattner noted that this extra funding allowed NCI to establish 'a fairly high powered immunologic capability through an interagency agreement with the Uniformed Services University [for the Health Sciences] ... One of the things that we were able to do through this mechanism was to develop a lot of immunologic assays. We also bought a FACS machine. A FACS machine is used for identifying T-cell subsets and, in retrospect, was one of the key instruments that helped us recognize the extent of the problem caused by AIDS'.[25] Goedert set up a pilot study of fifteen gay men in Manhattan and used the FACS machine to analyze their T cells. 'Essentially', Goedert said, 'we characterized the CD4 and CD8 populations' and 'came up with the startling discovery that half of the asymptomatic New York men were immunologically abnormal ...'[26]

A mistake made by the Goedert-Blattner group in seeking a cause for the new disease highlights the limits of practical immunological knowledge in the early 1980s. Their study also showed an apparent connection between the immune deficiency and the use of amyl nitrites by the study population. 'We went wrong in our analysis in that paper', Blattner stated. In retrospect, the use of these drugs 'was a mark of a high risk behavior for HIV infection' rather than a direct link between the drugs and the disease. 'You have to understand that when you are going through this kind of process and living it, as opposed to looking back on it, things were not that clear. There were very few of us who were living it, because there were not very many people working in the area. It is very clear to people in retrospect how 'stupid' we were, but ultimately the problem got solved through the process of scientific research'.[27]

On 15 January 1982, a second AIDS patient arrived at the Clinical Center and was taken into the protocol on Human Immune Problems investigated by Fauci. For this and later patients, Fauci, his postdoctoral fellow H. Clifford Lane, and Henry Masur, Chief of Critical Care Medicine in the Clinical Center, formed a core team to study the pathogenesis of AIDS while they tried to help these very sick patients.

Henry Masur, son of the first director of the NIH Clinical Center, Jack Masur, was an expert in infectious diseases in New York and had already seen AIDS cases when he was enticed to come to Bethesda to take over the Critical Care Service in the NIH Clinical Center. He had published one of the first articles about AIDS in the *New England Journal of Medicine* and wrote the first formal protocol for AIDS patients at the NIH. He described the way NIH investigators at the Clinical Center addressed the research problem and the sick patients:

> When we first started studying AIDS, we found – just by word of mouth – that there were a lot of people who wanted to look at various aspects of it ... It really took a combination of basic science and clinical science to bring the patients in, to recognize the important patient-care related problems, but also to do, very quickly, a lot of the ground work in immunology and virology. It required the range of expertise that we have at NIH from basic immunology, basic retroviral studies, basic herpes virus studies to very good autopsy studies. From the study group that we had, we got autopsies on patients to figure out what the range of the pathology was. The ophthalmologies were interesting. They enucleated all the patients who died, so they very quickly recognized what the retinitis was all about. Because there were people here who were free to choose what they wanted to do, who had the resources to devote to it and the esoteric backgrounds to take advantage of it, it all worked out.[28]

In 1982, H. Clifford Lane was a postdoctoral fellow in Fauci's laboratory of Immunology. As such, he was in closest contact with the patients on which he and Fauci worked. As they began to study patients with the then-unknown disease, he stated,

> ... we knew there was a T-cell defect and that there was a numerical decrease in the helper cells – that had been published. But what struck me ... – no one had really looked at this – was the amazing polyclonal B-cell activation. The B-cells of these patients were just incredibly turned on, more so than in lupus patients. This was something that I had been studying in normal volunteers. I had been looking at some autoimmune diseases, but this B-cell hyper-reactivity was something that superseded any of it; so I got very interested.[29]

Among the early AIDS patients was one who had an identical twin who was not sick. This offered the possibility for both treatment and research, because lymphocytes and marrow could be taken from the healthy twin and given to the patient without fear of a pathologic reaction. Lane observed,

> We watched with great excitement, because we saw the T4 count come up in the patient after we infused the lymphocytes; then it went right back down. Then, after we did the bone marrow transplant, the T4 count came up and it stayed up for a while... We were monitoring skin tests. The skin test response was getting bigger, and the T4 count was going up. So we were ecstatic. But then the T4 count started going down. The patient developed Kaposi's sarcoma, after which he developed cytomegalovirus [CMV] retinitis.

Lane spent hours every day in the patient's room explaining

> ... what we had done that day, what the lymphocytes were doing ... It was mind-boggling looking at how immunodeficient these patients were ... We would immunize the AIDS patients, and they would have no reaction ... At that time, we didn't have flow cytometry the way we do now. We were doing laborious physical techniques, like separating the helper cells from the suppressor cells. We were studying them separately because people thought there was too much suppression with the imbalance in the helper-suppressor ratio ... Clearly that wasn't the case. You could tell. The suppressor cells were there, in fact, they should have functioned normally, but they couldn't without normal inductive signals. It was the lack of that inductive signal from the helper cell that was the defect.[30]

Fauci and Lane continued their immunological studies of AIDS – indeed, the program still goes on today, and Fauci became the NIH's key spokesperson for AIDS and undisputed expert on its pathogenesis. His friend and colleague, John Gallin, now director of the NIH Clinical Center but director of intramural research at NIAID from 1985 to 1994, placed great hope in molecular immunology as the source of a therapeutic intervention in AIDS. In 1993, he speculated:

> In terms of therapeutics, I think the use of immuno-stimulants in this disease is emerging as a very exciting area that you are going to read about in the next few months. In particular, I am excited about Cliff Lane's current studies suggesting interleukin-2 is capable of reconstituting CD4 cell numbers in patients with AIDS. These cells are the principal ones attacked by HIV, and when they drop below a certain number the patient becomes highly susceptible to opportunistic infections like *Pneumocystis*. What Dr. Lane has found is that if you give patients IL-2 in the right way—it is very critical thing what the right way is—the fall in CD4 T-cell counts is reversed. I think the use of IL-2 and other immune cytokines, such as gamma interferon, IL-10, or IL-12, in the management of patients with AIDS and other immune disorders is going to be very exciting in the next few years. It will have broad implications beyond AIDS. [31]

So far interleukin-2 alone has proved useful as one part of a treatment strategy for people infected with the AIDS virus.[32]

One interesting detail of early pathogenesis studies was the fact that investigators ignored the problem of a second receptor for AIDS on human T cells as a problem that might help develop an intervention strategy. Early on, the CD4+ receptor was identified as the principal receptor through which the AIDS virus gained access to T cells. Mice, however, were known to exhibit CD4+ receptors on their T cells, yet they did not get AIDS. This indicated that a second mechanism involved in the entry process, probably a second receptor, had to exist on human cells. Virtually no research seeking this second receptor was done until the mid-1990s, when the field of receptor biology intersected with the study of cytokine biology to produce the discovery in 1996 of the second receptor of HIV, CCR5.[33] This work led to exciting projections that a cure for AIDS might be imminent, but, of course, they were premature.

At the end of 1982 and the beginning of 1983, Robert C. Gallo's Laboratory of Tumor Biology in NCI began a search for the etiological agent of AIDS at the behest of James Curran, who headed the epidemiological work on AIDS at the CDC and urged Gallo as a virologist to investigate the new disease.[34] Gallo's decision to respond to Curran's suggestion grew out of the immunological information suggesting that AIDS might be related to his own previous research. Abnormal numbers of helper and suppressor T cells were the first immunological manifestation of the disease to be documented, and once AIDS had been epidemiologically determined to be transmissible, which occurred in mid-1982, work on AIDS etiology was guided by the assumption that the unknown agent would be something that attacked T cells. The only such agent known was a newly discovered class of human retroviruses, HTLV-I and HTLV-II, identified in 1980 by Gallo and his colleagues.[35] These retroviruses, however, caused uncontrolled growth in the T cells, producing T-cell leukemia. Although the pathogenic process was reversed in AIDS, in that T cells were dying instead of proliferating, the investigators worldwide who began to search for an AIDS agent were primarily retrovirologists looking for a

retrovirus because the intellectual framework in which they had been schooled predicted that such an organism would be the cause.[36]

Similarly, research on the initial therapy with any effectiveness against AIDS, azidothymidine, or AZT, sold under the brand name Retrovir®, was conducted within the molecular knowledge about the AIDS virus's genetic makeup and life cycle that emerged in the months after the virus was identified (Figure 11.4). The only point of intervention that appeared immediately vulnerable to possible rational drug design in the mid-1980s was the step in which the ribonucleic acid (RNA) of the virus was transcribed into deoxyribonucleic acid (DNA) that could be incorporated into the cell's DNA. The enzyme that guided this process, reverse transcriptase, was known, and drugs that might inhibit its action were investigated by Samual Broder and his colleagues via the NCI's drug screening program. AZT was the first promising drug identified that was sufficiently low in toxicity that human patients could tolerate it. It ultimately proved to be less effective than originally indicated, but as the first hopeful therapy for AIDS, it inspired new research within the molecular paradigm.[37]

In conclusion, the emerging paradigm of molecular immunology provided the framework for understanding and investigating the emerging disease, AIDS. This phenomenon was not limited to the approach taken by the intramural program at the National Institutes of Health but was the case worldwide. The earliest attempts at the NIH to understand AIDS revealed not only the power of this emerging paradigm to frame the new epidemic disease but also the limitations of its development at that moment in time. This case study, detailing how intellectual concepts in biomedical

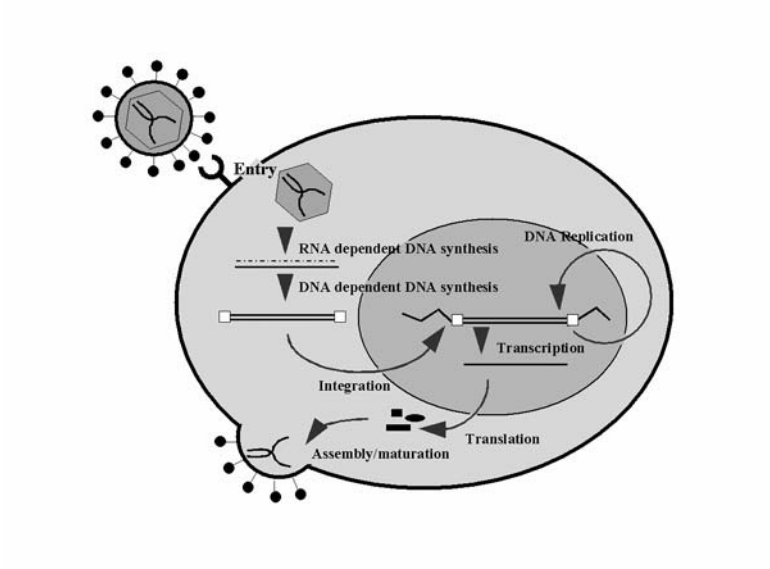

Figure 11.4 Diagram of life cycle of Human Immunodeficiency Virus, showing major points at which interventions might be successfully developed. Figure courtesy of Vinay K. Pathak, Ph.D., Chief, Viral Mutation Section, HIV Drug Resistance Program, National Cancer Institute, National Institutes of Health, Bethesda, MD.

research shape the response to new diseases, also demonstrates the flow of information in the opposite direction, as research on one disease speeds the elucidation of the intellectual concept itself.

Notes

1 The website is <http://www.history.nih.gov/NIHInOwnWords/> accessed 4 October 2006. Previous studies include Victoria A. Harden, 'The Biomedical Response to AIDS in Historical Perspective', in Victoria A. Harden and Guenter B. Risse (eds), *AIDS and the Historian*, *Proceedings of a Conference at the National Institutes of Health 20–21 March 1989*, Washington, D.C.: US Department of Health and Human Services, Public Health Service, National Institutes of Health (NIH Publication No. 91-1584), 1991, pp. 36–40; idem, 'Koch's Postulates and the Etiology of AIDS: An Historical Perspective', *History and Philosophy of the Life Sciences*, 14, 1992, pp. 245–65; idem, 'The NIH and Biomedical Research on AIDS', in Caroline Hannaway, Victoria A. Harden, and John Parascandola (eds), *AIDS and the Public Debate: Historical and Contemporary Perspectives*, Amsterdam: IOS Press, 1995, pp. 30–46; idem, 'The Scientific Construction of New Diseases: Rocky Mountain Spotted Fever and AIDS as Comparative Case Studies', in Martha L. Hildreth and Bruce T. Moran (eds), *Disease and Medical Care in the Mountain West: Essays on Region, History, and Practice*, Reno: University of Nevada Press, 1998, pp. 59–71.

2 '*Pneumocystis* Pneumonia – Los Angeles', *Morbidity and Mortality Weekly Reports* (hereafter *MMWR*), **30**, 5 June 1981, pp. 250–2.

3 'Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men – New York City and California ', *MMWR*, **30**, 3 July 1981, pp. 305–8.

4 'Follow Up on Kaposi's Sarcoma and *Pneumocystis P*neumonia', *MMWR*, **30**, 28 August 1981, pp. 409–10.

5 On changes in PHS and its agencies in the 1960s and 1970s, see Fitzhugh Mullan, *Plagues and Politics: The Story of the United States Public Health Service,* New York: Basic Books, 1989, pp. 146–92. In the summer of 1981, Edward N. Brandt, M.D., served as Assistant Secretary for Health, having assumed the position on 14 May 1981. The post of Surgeon General was vacant. C. Everett Koop, M.D. had been selected, but his Senate confirmation was contentious throughout the summer of 1981. He was finally confirmed on 16 November 1981. See *NIH Almanac, 2001*, National Institutes of Health, 2001 (NIH Publication No. 01-5), p. 62.

6 See, for example, Randy Shilts, *And the Band Played On: Politics, People, and the AIDS Epidemic,* New York: St. Martin's Press, 1987; Sandra Panem and Samuel O. Thier, *The AIDS Bureaucracy,* Cambridge, MA: Harvard University Press, 1988; Bruce Nussbaum, *Good Intentions: How Big Business and the Medical Establishment Are Corrupting the Fight Against AIDS,* New York: Atlantic Monthly Press, 1990.

7 Victoria A. Harden and Dennis Rodrigues, 'Context for a New Disease: Aspects of Biomedical Research Policy in the United States before AIDS', in Virginia Berridge and Philip Strong (eds), *AIDS and Contemporary History,* Cambridge: Cambridge University Press, 1993, pp. 182–202.

8 Ibid.; Richard Mandel, *A Half Century of Peer Review, 1946–1996*, Bethesda, Maryland: National Institutes of Health, Division of Research Grants, 1996. This is one of several sources utilized in this paper that were 'privately published' by the NIH, which had an exemption from Congress to print materials outside the Government Printing Office (for more examples,

see notes 14 and 21). Daniel M. Fox, 'The Politics of the NIH Extramural Programme, 1937–1950', *Journal of the History of Medicine and Allied Sciences*, **42,** 1987, pp. 447–66. For the AIDS activists' view, see Larry Kramer, *Reports from the Holocaust: The Story of an AIDS Activist*, updated and expanded edition, New York: St. Martin's Press, 1994, pp. 39–40, 61, 80–1.

9 Melissa K. Klein, 'The Legacy of the "Yellow Berets": The Vietnam War, the Doctor Draft, and the NIH Associate Training Programme', manuscript, 1998, Office of NIH History, National Institutes of Health, <http://history.nih.gov/history/Yellow%20Berets1.pdf> accessed 31 May 2004.

10 Buhm Soon Park, 'The Development of the Intramural Programme at the National Institutes of Health after World War II', *Perspectives in Biology and Medicine,* **46**, 2003, pp. 383–402.

11 On the history of advances in molecular immunology, see Peter Keating and Alberto Cambrosio, *Biomedical Platforms: Realigning the Normal and the Pathological in Late-Twentieth-Century Medicine,* Cambridge, MA: MIT Press, 2003; *New Initiatives in Immunology: NIAID Study Group Report,* Washington, DC: US Department of Health and Human Services, Public Health Service, National Institutes of Health, 1981 (NIH Publication No. 81-2215); Debra Jan Bibel, *Milestones in Immunology: A Historical Exploration,* Madison, WI: Science Tech Publications, 1981; Arthur M. Silverstein, *A History of Immunology,* San Diego, CA: Academic Press, 1989.

12 Victoria A. Harden and Dennis Rodrigues, interview with Thomas Waldmann, 14 March 1990, National Institutes of Health, Bethesda, MD; copy available at <http://www.history.nih.gov/NIHInOwnWords/assets/media/pdf/Waldmann90.pdf> accessed 4 October 2006.

13 E.J. Holborow and W.G. Reeves, *Immunology in Medicine,* London: Academic Press, 1977, p. ix.

14 Lydia Woods Schindler, 'Understanding the Immune System', no publication data provided, 13 pp. This publication was a cooperative project between the NIAID and the NCI.

15 Stanley Cohen, Edgar Pick, and Joost J. Oppenheim (eds), *Biology of the Lymphokines,* New York: Academic Press, 1979, p. 4.

16 MEDLINE search for 'T cell' and 'B cell' in title field of AIDS databases, 1981–1990. For the history of flow cytometry and the FACS machine, see Alberto Cambrosio and Peter Keating, 'A Matter of FACS: Constituting Novel Entities in Immunology', *Medical Anthropology Quarterly*, **6**, 1992, pp. 362–84; idem, *Exquisite Specificity: The Monoclonal Antibody Revolution,* New York: Oxford University Press, 1995; Alberto Cambrosio, Peter Keating, and R.D. Guttmann, 'New Medical Techologies and Clinical Practice: A Survey of Lymphocyte Subset Monitoring', *Clinical Transplantation*, **8**, 1994, pp. 532–40; Peter Keating and Alberto Cambrosio, '"Ours is an Engineering Approach": Flow Cytometry and the Constitution of Human T Cell Subsets', *Journal of the History of Biology*, **27**, 1994, pp. 449–79; idem, 'Interlaboratory Life: Regulating Flow Cytometry', in Jean-Paul Gaudillière and Ilana Löwy (eds), *The Invisible Industrialist: Manufacturers and the Construction of Scientific Knowledge,* London: Macmillan, 1998, pp. 250–95.

17 MEDLINE searches for 'FACS' and 'PCR' in title field of AIDS databases, 1981–1990. On the history of PCR, see Paul Rabinow, *Making PCR: A Story of Biotechnology,* Chicago: University of Chicago Press, 1996; Kary Mullis, *Dancing Naked in the Mind Field*, New York: Pantheon Books, 1998; the National Museum of American History also holds extensive documentation of the history of the polymerase chain reaction. See <http://www.si.edu/archives/ihd/videocatalog/9577.htm> accessed 26 July 2006.

18 PDP stands for 'Programmable Data Processor'. The PDP-11 was a 16-bit machine produced from 1970 to 1990 and widely used in laboratories throughout that period. For a history of these computers, see <http://www.pdp11.org/> accessed 13 December 2004.

19 P.H. Bartels and G.B. Olsen, 'Computer Analysis of Lymphocyte Images', in Nicholas Catsimpoolas (ed.), *Methods of Cell Separation,* vol. 3, New York: Plenum Press, 1980, p. 9.

20 Harden, 'The Scientific Construction of New Diseases' (n. 1); Keating and Cambrosio, *Biomedical Platforms* (n. 11); Mark Bowers, 'A History of Chemokines' and 'Chemokines and HIV', *Bulletin of Experimental Treatment for AIDS*, March 1977, <http://www.aegis.org/pubs/beta/1997/BE970310.htm> accessed 26 July 2006.

21 Victoria A. Harden interview with Richard Krause, 17 November 1988, National Institutes of Health, Bethesda, Maryland; accessed 4 October 2006 at <http://www.history.nih.gov/NIHInOwnWords/assets/media/pdf/Krause88.pdf>; Victoria A. Harden, interview with Anthony S. Fauci, 7 March 1989, accessed 4 October 2006 at <http://www.history.nih.gov/NIHInOwnWords/assets/media/pdf/Fauci89.pdf>; Harriet R. Greenwald and Victoria A. Harden (eds), *Intramural Contributions, 1887–1987*, Bethesda, Maryland: National Institute of Allergy and Infectious Diseases, 1987, accessed 4 October 2006 at <http://history.nih.gov/history/NIAID_Intramural_Contributions.pdf>. The history of Fauci's laboratory is on p. 117. For biographical information on Fauci, see <http://www.niaid.nih.gov/director/director.htm> accessed 4 October 2006. In 1980, NIAID created the Laboratory of Immunoregulation for Fauci, 'to apply new knowledge in immunology to the clinical diagnosis and treatment of patients with immunological disorders'. It was one of seven new laboratories created between 1977 and 1987 in molecular medicine.

22 Waldmann interview (n. 12).

23 For biographical information on Waldmann, see <http://ccr.cancer.gov/staff/staff.asp?profileid=5774> accessed 4 October 4, 2006.

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35 Robert C. Gallo, *Virus Hunting: AIDS, Cancer, and the Human Retrovirus: A Story of Scientific Discovery*, New York: New Republic Book of Basic Books, 1991, pp. 59–124; see also information on Gallo's Lasker Basic Medical Research Prize in 1982 at <http://www.laskerfoundation.org/awards/library/1982basic.shtml> accessed 4 October 2006.

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CHAPTER TWELVE

Conceptualizing the Maternal-Fetal Relationship in Reproductive Immunology

Moira Howes

> We have learnt much about the mother's immunological intolerance of its foetus … It will be as well to be aware of these dangers, even if there is an inclination to make too much of them: for even if we set down all the known causes of antenatal mortality or miscarriage, the unexplained residue is of stirring proportions … [There] is clear evidence of the fundamental advances in our knowledge of the relationship between mother and foetus that may yet emerge from a deliberate study of its shortcomings.[1]

Introduction

Immunological phenomena are increasingly thought responsible for a variety of fertility and pregnancy problems. From reports that suggest having a male baby increases one's future risk of fetal loss, to those that suggest women can identify the scent of reproductively compatible men, immunology is implicated.[2] Immunology has, in fact, been referred to as the 'new area of infertility treatment for this century'.[3] And indeed, some women are already turning to immunology for help. Notably, *The New York Times* recently reported that a woman spent $300,000 (USD) on fertility treatments, some immunological, in order to have a second baby.[4] While much remains to be discovered about the immunology of reproduction, scientists and the public are becoming quite excited about its potential applications.

The excitement over the potential of immunology to enhance fertility is troublesome, however. New immunotherapies for infertility stand on shaky empirical ground, especially when contextualized against the persistence of doubts about allergy immunotherapies over the last hundred odd years.[5] Currently, no clear evidence exists to show that immunological tests and treatments increase the likelihood of successful pregnancy. Diagnostic tests are not standardized and laboratory discriminations of what is normal and pathological do not translate well into actual fertility problems.[6] Are antibodies to sperm normal or pathological? Do high levels of antibodies directed against a woman's own self components cause infertility? No one really knows. In the meantime, an increasing number of women are paying to have these things measured.

But money spent however unwisely is a minimal concern in light of the evidence that the health of women may be negatively affected by immunological treatments.[7] The health of their newborns may also be affected. Immunological (and non-immunological) fertility treatments pose risks of serious immunological problems including graft versus

host reactions (like those in organ transplant rejection), the induction or exacerbation of autoimmune diseases (such as lupus), changes in allergic responses, and alloimmune neutropenia in newborns.[8] At a more theoretical level, it is worrisome that these tests and treatments are offered to women at all, given that the reasons for observed differences in immunity between the sexes remain unclear. Women have higher levels of immune activity and allergies than do men and they constitute the vast majority of autoimmune disease sufferers.[9] Without knowing why these differences exist, immunological tests and treatments for infertility pose unknown risks.

Feminists have identified many reasons for the tunnel-vision and occasional recklessness of the fertility industry – money, power, ignorance, pro-natalism, as well as problematic attitudes about and towards mothers and women generally. Fertility treatments based on reproductive immunology may also be influenced by these factors. At present, however, my concern is the degree to which certain theoretical assumptions and experimental practices shape models of the maternal-fetal immunological relationship. How immunologists conceive of this relationship is relevant to our knowledge of the risks to which women and their newborns are exposed by this new area of infertility treatment. For example, if a seriously incomplete model of maternal-fetal immunological relations dominates research, and hypotheses about treatments are based on this model, then the treatments developed may be ineffective or even harmful to health. Unquestioned acceptance of a dominant model can lead to overconfidence, which may in turn contribute to the hasty implementation of treatments. When a scientific model matches with social values and expectations, the perception that the model mirrors reality may be strengthened, making it more difficult to evaluate critically treatment programs that are based on the model. So, for example, if an immunological model assumes that women are biologically passive in pregnancy, and certain societal values also regard women as socially passive in pregnancy, problems associated with the assumption of passivity may be less visible. Sorting out conceptual difficulties in models of the maternal-fetal relationship is one way to gain understanding and potentially lessen the immunological risks posed to women and their pregnancies.

My suggestion is that a seriously incomplete model of maternal-fetal immunological relations has, in fact, dominated research, and that exploring alternatives to this model may encourage new perspectives of maternal-fetal immunological relations. The spectrum of possible conceptualizations of the maternal-fetal relationship has already been explored in feminist analyses, so it is helpful to use the conceptual models they have produced. Feminist analyses descriptively and prescriptively investigate at least three ontological models of the maternal-fetal relationship. The first, which I call the 'foreign-fetus model', holds that mothers and their fetuses are two separate entities; the physical connection between them is thus de-emphasized or ignored.[10] The second, which I call the 'body-part model', holds that the fetus is the mother's flesh, or is a part of the mother in much the way that the mother's kidney is a part of her.[11] In the third model – the 'not-one-but-not-two model' – the distinctions between mother and fetus are blurry and develop over time.[12] Mother and fetus are neither two distinct individuals, nor do they count as one distinct individual. In this model, relations between mother and fetus are interconnected and dynamic, and the gradual physical differentiation of mother and fetus is emphasized.

Each of these ontological models has an immunological counterpart, though one model – the foreign-fetus model – clearly dominates the field of reproductive immunology. The immunological foreign-fetus model contains two particularly problematic assumptions, and together these significantly shape theoretical and experimental practice. The first assumption is the view that mothers and fetuses are clearly distinct entities separated by an immunological barrier. The second is that if there is a breakdown in this barrier, the maternal immune system will respond antagonistically to the fetus. Thus, while it may be that 'there is something unnatural about positing a fetus at odds with its own mother, since until recently pregnancy was viewed as a cooperative interaction',[13] this cannot be said of immunology, as maternal-fetal immunological relations have not, generally speaking, been viewed as cooperative.

In my first section, I outline the foreign-fetus model in immunological theory. This outline will make explicit the assumptions of maternal-fetal distinctness and antagonism as well as problematic understandings of maternal *reactivity* towards the fetus or diseased tissue. I argue that maternal immune reactivity is cast as either passive or pathological; thus, active, beneficial maternal involvement is marginalized. I also argue that the restriction of maternal reactivity to the passive and pathological directs experimental practice in reproductive immunology into two problematic frameworks: pathology and organ transplantation. Thus, it is vital to consider experimental practice because these problematic assumptions are instantiated in material practice. Next, I examine another immunological model of maternal-fetal relations based on Polly Matzinger's (1994) danger theory.[14] This model is analogous to the body-part model in philosophy, and thus helps to show what a departure from the standard foreign-fetus model might look like from theoretical and experimental perspectives. But while the danger model of maternal-fetal relations takes a provocative step in the right direction, it does not do quite enough to render explicit the positive maternal immunological involvement in pregnancy. Finally, I propose that there is a need for a model that takes a 'not-one-but-not-two' approach to immune selfhood that centralizes beneficial maternal immunological contributions to pregnancy. The seeds of this model are already present in reproductive immunology, but they need to be developed. I refer to this model as the *relational* model, for it simultaneously recognizes that immune contact occurs between mother and fetus and explicitly adopts the view that maternal immune activity is primarily beneficial and constructive to pregnancy.

It is important to note here that the relational model does not deny that immunological conflict and indifference exists in the maternal-fetal biological relationship. Rather, it denies that immunological conflict and indifference themselves provide an adequate picture of pregnancy immunology. The relational model suggests that the maternal immunological activities beneficial to the progress of pregnancy are much more important than previously regarded. I emphasize the beneficial and constructive elements of the maternal immune system quite strongly, in part to draw attention to this lacuna in the immunology of pregnancy. But this emphasis should not be taken to imply that maternal-fetal immunological relations are exclusively beneficial.

I also do not want the relational model to be taken to imply that women should necessarily experience their fetuses in a harmonious manner and wish to benefit them. I am not suggesting that we adopt a naively optimistic view of women's experience of pregnancy. Nor does biology, immunology in particular, dictate this sort of psychological

experience of the fetus. A woman may justifiably feel, as many have felt, that the fetus is an utterly foreign invader.[15] I discuss the relational model, not to advocate a certain experience of pregnancy, but because it expands the range of values available for reasoning in immunology and augments critical awareness of the influence of values on this field. So, though I argue that the foreign-fetus model in reproductive immunology is problematic and that the relational model is an antidote of sorts, I do not make this same argument with respect to women's experience of pregnancy. I restrict my arguments and the implications of my arguments to immunology.

In essence, I offer a description of immunological models currently used in reproductive immunology and their philosophical correlates. I complement this description with a critique showing that the foreign-fetus model is outmoded – at best, it provides an incomplete account of maternal immunological activities. The danger model, though an improvement, does not do enough to model positive maternal immunological responses. The relational model is conceptually the best available – it can accommodate the full spectrum of maternal immunological functions – but it has no clearly developed immunological correlate. My overall objective is to argue for the importance of this third approach to maternal-fetal relations in reproductive immunology. In so doing, I show that there remains a strong need for feminist critiques of science, especially those that engage experimental practice.[16]

The Foreign-Fetus Model of Pregnancy Immunology

The foreign-fetus model of maternal-fetal immunological relations is largely a consequence of the view that self-nonself discrimination is the primary organizing principle of the immune response. Self-nonself discrimination is the means by which the immune system learns to kill nonself invaders without harming self components. However, the source of problematic assumptions about the maternal-fetal immunological relationship is not so much *that* a self is posited; rather, it is the *kind* of self implicitly assumed.[17] The most prevalent view of the immune self assumes that it is sharply defined, unitary, independent, masculine, and Western.[18] But this understanding of selfhood poses a problem for pregnancy. If the 'selves' involved in pregnancy are static, unitary, and fully independent, this will restrict the sorts of immunological relationships thought possible between them. Given the strict self-guarding immune activities required to maintain sharp self-definition, contact between the unitary selves of mother and fetus is most naturally understood in terms of conflict or submission. There is little room for mutually beneficial relations.

The sharply defined immune self generates all sorts of theoretical problems and experimental anomalies, and for this reason, it is tempting to reject the notion of immune selfhood altogether. However, this rejection sits uncomfortably with empirical evidence that shows that some degree of immunological individuality exists.[19] The task is to construct an understanding of selfhood between the extremes of a purely and sharply defined self and the absence of self; and here, pregnancy could be a guide, rather than an exception. Pregnancy suggests a developmental and relational understanding of immune selfhood, and an immune self with flexible, blurry edges. This ontological claim better fits the nature of biological individuality in general, given that organisms negotiate individuality in ways that often do not fit precise philosophical criteria. Conjoined

twins, for example, violate philosophical criteria that individuate persons on the basis of the unitary body. But note that while ontology is by no means irrelevant to human experience, the ontological status of pregnancy here advanced does not determine what women's experience of pregnancy must be. Given the flexibility of the selfhood relations involved, a variety of experiences of pregnancy are compatible with it.

Despite being a potential source of enlightenment about immune selfhood, however, pregnancy has instead been forced to fit a unitary self model that admits no more than one individual. This has significant consequences for pregnancy immunology. According to self-nonself discrimination theory, the mother's immune system should classify the fetus as nonself, for the fetus is an 'an antigenically foreign body, a kind of foreign graft'.[20] Thus, if the mother's immune system recognizes the fetus, it should eliminate it. But this does not happen. As Peter Medawar notes, the fetus does not 'immunize the mother'; if it did, the consequences would be 'disastrous to itself'.[21] Following Medawar, immunologists refer to this mysterious tolerance of the fetus as the 'immunological paradox of pregnancy'.

This paradox does make one wonder how the fetus evades hostile maternal forces. Various proposals, the earliest of which came from Medawar, have been put forth to explain why self-nonself discrimination between mother and fetus does not more frequently lead to harm. Medawar offers three explanations, and, though none would be wholly accepted today, there is some truth in each.[22] His first explanation is that the fetus might have immature antigens that fail to stimulate the maternal immune system. His second is that an anatomical barrier, perhaps provided by a 'vascular quarantine', may prevent maternal-fetal contact.[23] Medawar's third explanation is that mothers might be immunologically inert or idle during pregnancy. He suggests that the excess cortisone production brought on by endocrinological changes during pregnancy leads to a general suppression of the maternal immune system.[24]

Medawar's preoccupation with immunological identity is understandable: in addition to his skin transplantation experiments, the then-new discovery that immunological conflicts were behind hemolytic diseases of the newborn (such as Rh disease) provided evidence for immunological incompatibility between biological individuals. Hemolytic diseases of the newborn also provided inspiration: the idea that pathology could result from immunological contact between mother and fetus was a striking one. However, the fact that hemolytic diseases are ultimately caused by immunological contact between mother and fetus means that contact does occur. Though puzzled by this contact, Medawar is aware that mothers transfer antibodies to their fetuses.[25] He says,

> the antibodies which are the chemical effectors of the immunity reaction must be able to pass from the mother's circulation into the circulation of the unborn child. In effect, this means that the membranes which separate mother from foetus must be of such a kind as to let the antibodies through.[26]

There is tension, then, between Medawar's demand for a barrier, whether anatomical or regulatory in nature, and the various instances of its violation.

This same tension still exists today. In a text concerning the maternal-fetal immunological relationship and cell-surface markers known as human leucocyte antigens (HLA), immunologist Joan Hunt says:

> The mammalian maternal-fetal interface is a battleground where warring factions struggle for control. Here, because of an evolutionary decision to internalize the embryo, the reproductive and immune systems are brought into direct conflict … The unexpected willingness of mothers to accept genetically disparate tissues has often been described as the 'immunological paradox' of pregnancy.[27]

Shortly after this she continues: 'a less well recognized but equally surprisingly aspect of pregnancy is that a certain measure of maternal immune recognition [of the fetus] increases fertility'.[28] On the one hand, then, maternal recognition of the fetus leads to harmful responses that will decrease the success of implantation or pregnancy and thus, fertility. On the other, maternal recognition of the fetus leads to beneficial responses that increase the success of implantation and pregnancy – and hence, fertility (here defined as the ability to conceive and complete a pregnancy). It is *surprising* that maternal immune responses increase fertility because it has long been assumed that maternal responses are antagonistic in nature. That such tension exists reflects how poorly the idea of beneficial maternal immunological contribution to pregnancy fits self-nonself discrimination theory.

Contemporary hypotheses for the 'surprising' tolerance of the fetus share basic features with Medawar's original proposals. For example, one contemporary hypothesis is that maternal-fetal conflict is controlled by mechanisms that hide or conceal the fetal trophoblast from the maternal immune system, in effect achieving a local immunosuppression.[29] The proposed mechanism of concealment involves the major histocompatibility complex Class I genes.[30] These histocompatibility genes code for the HLA found on most cells of the body and are involved in rejecting nonself tissues from the body – hence the need for a close match between organ donors and recipients. In fetal trophoblast cells, however, the HLA differ from that of the average body cell. The usual types of HLA are down-regulated and so do not appear on the cell surface and unusual HLA molecules are produced instead. Thus, the molecules that one would expect to identify fetal trophoblast cells to the maternal immune system are either absent or altered. Trophoblast concealment might also be achieved through the initiation of programmed cell death in maternal immune cells capable of recognizing the fetus.[31] This would explain why maternal T and B lymphocytes that target the paternal antigens present in fetal cells do not appear to inhabit uterine tissues in significant numbers.[32]

Systemic maternal immunosuppression is the basis of another contemporary hypothesis for the control of maternal-fetal conflict. Though controversial, some immunologists think systemic immunosuppression may be achieved by something known as 'Th2 bias', which involves a shift in cytokine[33] profiles from those produced by T-helper 1 lymphocytes to those produced by T-helper 2 lymphocytes.[34] This hypothesis bears some resemblance to the general proposal that in pregnancy, the innate immune system is activated while specific immune responses are suppressed.[35] The specific arm of the immune system attacks using highly specific molecular recognition; and, while this is great for fighting pathogens, highly specific recognition of the fetus is thought to be dangerous. On this view, then, system-wide maternal immunosuppression is achieved by very general changes in immunoregulation.

These contemporary hypotheses for maternal immunosuppression and fetal concealment are certainly intriguing, but their adequacy is by no means established.

From an evolutionary perspective, it is difficult to see how systemic suppression of specific immunity could persist in vertebrates. The need to protect against infection certainly does not decrease in pregnancy – if anything, it increases. And, given the complex interrelationships between innate and specific immunity, locating suppression in one or other of the compartments may not be possible. Indeed, research increasingly challenges the existence of a clear innate-specific distinction.[36] And, though pregnant women do show differences in immune function, they are clearly not globally deficient in specific immune functions. Changes in immunoregulation may be more fine-grained and restricted than is suggested by Th2 bias.

Immunosuppression hypotheses for maternal tolerance of the fetus also reveal both a preoccupation with traditional understandings of self-nonself discrimination and problematic assumptions about the nature of maternal reactivity towards the fetus. These assumptions about maternal reactivity intersect with notions of the ideal unitary independent self – and the connections between selfhood and biological reactivity run deep in the scientific context out of which immunology grew. In the late nineteenth century, who you were was considered relevant to your degree of reactivity to the environment. Mark Jackson, for example, contends that upper class white men were thought to suffer more from hay fever and asthma because of their status. The cultural and intellectual superiority of such men caused them to react strongly to things natural and uncivilized. Class, race and gender stratification thus influenced the emergence of the allergy concept in the early twentieth century.[37] As allergies became more prevalent, however, it became more clear that women, those of 'other' races, and the poor did suffer from allergies; indeed, it was soon thought that more women than men suffered from this condition. Jackson, however, contends that explanations for this gender difference preserved the social hierarchy present in earlier explanations. Women had more allergies because of their domesticity – that is to say, their closeness to house dust and cleaning solutions.[38]

Connections between self and reactivity also exist in emerging explanations of inflammation in the first part of the twentieth century. Ohad Parnes argues that allergy and autoimmune disease were then understood as instances of misdirected inflammation and were rooted in conceptions of reactivity from the field of pathology.[39] Inflammation was understood as reactivity that repaired the body; but, inflammatory diseases, some of which we now classify as autoimmune, were understood as examples of inappropriate, self-destructive reactivity. The spectrum of inflammatory reactivity, then, ranged from the reparative, through the defensive, to the destructive.

The key difference between maternal reactivity and the tradition of ideas about reactive inflammation in pathology and immunology – and indeed, earlier ideas about reactivity in allergy as well – is that maternal reactivity is not conceptualized as reparative. The maternal immune system is either locally or systemically suppressed in the process of pregnancy, which passively allows the fetus to invade, or it is inappropriately or pathologically reactive, in which case the mother rejects the fetus and, in more recent hypotheses, the sperm of her male partner.[40] In cases of recurrent pregnancy loss thought to have an immunological cause, women are considered inappropriately reactive to fetuses. In cases of sperm allergy or 'hostile' cervical 'mucus', women are considered inappropriately reactive to (se)men.[41] Inappropriate reactivity to semen has also been put forward as a cause of pre-eclampsia, a serious hypertensive condition related to

inadequate blood flow between mother and fetus. The hypothesis is that women who are immunologically 'unfamiliar' with their partner's sperm are more likely to develop this condition.[42] Familiarity with sperm is thought to suppress maternal-fetal conflict, which allows the fetus to fully invade and keep the blood supply open.

Missing here is the idea that women's immune systems are *constructively* reactive during pregnancy. Constructive maternal reactivity thus falls through a gap between passivity and pathology. This unduly restricts alternative hypotheses worthy of investigation. For example, in cases of recurrent pregnancy loss, it may be that the maternal immune system does not construct the necessary environment for fetal nutrition – an explanation quite different from that made available by the foreign-fetus model. Another example concerns the fact that after years of targeting inappropriate maternal immune activity as the suspected cause of recurrent pregnancy loss, an hypothesis has recently emerged that men may have a causal role due to certain deficiencies in their semen.[43] Here, men have not typically been considered causative agents. The emphasis on maternal harmfulness obscures consideration of potential paternal factors in recurrent pregnancy loss. Viewing maternal immunity as principally constructive may have opened space for hypotheses about the paternal role sooner.

The hypothesis that pre-eclampsia is due to maternal immunological unfamiliarity with the father's sperm is also worthy of challenge. Another hypothesis indicates a more straightforward route to pre-eclampsia. This hypothesis holds that bacterial vaginosis may be the culprit.[44] Here, pathogen defence during pregnancy results in pathology: but it is a constructive form of reactivity insofar as its goal is to control infection whilst maintaining a pregnancy. The relevance of pathogen defence to pregnancy immunology is not overlooked in this hypothesis. But I suspect it is overlooked in the hypothesis concerning maternal immune familiarity with sperm. The sperm familiarity hypothesis is somewhat counterintuitive, given its reliance on monogamy, and it does not take into account the role of infection. The bacterial vaginosis hypothesis is perhaps more plausible insofar as we know that it is relatively commonplace for women to deal with infections of the reproductive tract before, during and after pregnancy.

The type of reactivity assigned to pregnant women may, then, affect theory and practice in reproductive immunology. The restriction of maternal reactivity to the passive and pathological makes the foreign-fetus model particularly difficult to destabilize, especially given its conjunction with longstanding assumptions about the unitary immune self. What may make it even more difficult to destabilize, however, is its instantiation in the material practices of reproductive immunology. Now that some of the theoretical aspects of the foreign-fetus model have been made explicit, I turn to consider the ways in which these assumptions shape experimental practice in reproductive immunology.

The Foreign-Fetus Model in Experimental Practice

The stability of the foreign-fetus model is only partly explained by ontology and the social-historical context from which it emerged. The foreign-fetus model is also stabilized by experimental tools and methods developed over decades of research influenced by self-nonself discrimination theory. Loyalty to experimental practice plays an important role in conceptualizations of the maternal-fetal immunological relationship, for loyalty

may persist at least as long as experiments produce unusual results.[45] Certainly, the idea that maternal recognition of the fetus promotes healthy pregnancies is an unusual and welcome experimental result. Is it desirable, then, that experimental practices centred around foreignness and antagonism persist? For those troubled by the laboratory instantiation of concepts having unjust and erroneous foundations as well as adverse effects for women's health, the answer may well be 'no'. Moreover, in cases where experimental and theoretical systems are broken apart – that is, where they are *detachable* in some way from each other – it is possible for experimental practices to perpetuate approaches belonging to a given theoretical model even though that theoretical model has been rejected.[46] Destabilizing experimental loyalty thus demands an ongoing dialogue between theoretical and practical critique.

However, because the distinction between theory and experimental practice is somewhat blurred, it is not always possible to know where to assign responsibility for the persistence of problematic ideas. Instead, it is likely that many factors are at play, including 'data, theory, experiment, phenomenology, equipment, data processing' and so on.[47] There are also a variety of different traditions behind the types of equipment used and experiments performed.[48] Destabilizing loyalty to an experimental practice, especially in scientific cultures that demand constant and intense productive activity, is difficult. With the heavy emphasis on 'doing' in science, there is often little time to seriously rethink experimental methodologies – one just keeps using them. Destabilizing loyalty is also challenging because experimenters do not, 'as a rule, deal with isolated experiments in relation to a theory, but rather with a whole experimental arrangement designed to produce knowledge'.[49] The foreign-fetus model does not simply influence the odd experiment in reproductive immunology. If this were so, it would be highly disposable. Instead, it runs throughout experimental systems in reproductive immunology and interlocks with experimental models in immunology as a whole.

In this particular case, assumptions about maternal-fetal distinctness, antagonism and maternal reactivity help channel methodology into what I call the *pathology* and *transplantation* experimental frameworks. Each framework reflects just how deeply these assumptions influence reproductive immunology. This is not a wholly negative thing: something must anchor research, and immunologists in this area have a limited set of tools available to them. Because human pregnancy is physiologically unique in the animal world, it is difficult to find suitable animal models, and many studies in this area are therefore retrospective.[50] It is also understandable that the foreign-fetus model wields the influence it does given that self-nonself discrimination theory guides much of the experimental work in the field of immunology as a whole. It would be surprising if reproductive immunology was an exception. However, because the foreign-fetus model appears to impede the development of new experimental systems, it is important to make the theoretical factors shaping experimental practice – and the experimental factors perpetuating the foreign-fetus model – explicit.

The Pathology Framework

As my introductory quotation attests, the use of pathology as a tool in experimental investigation has a history in immunology. But while Medawar dismisses the concern that too much might be made of the shortcomings of the maternal-fetal relationship,

he is at least aware that such a concern exists. Most contemporary experimental models in reproductive immunology deliberately study the shortcomings of the maternal-fetal relationship with little or no apparent concern for this method's limitations. And now, too much *is* made of 'the mother's intolerance of its foetus'.

There are a few ways in which pathology is exploited in experimental reproductive immunology. Immunologists look, for instance, to problems experienced by women who are pregnant or who try unsuccessfully to become pregnant. Women who have recurrent pregnancy losses are therefore commonly used as clinical subjects in reproductive immunology, as are women with unexplained fertility problems and pre-eclampsia. Immunologists will observe or test these women for the existence or development of immunological problems before or after fertility treatments have been tried. Paternal leucocyte immunization is an example of a treatment for which this sort of information is sought. Ovarian stimulation, though not an immunological treatment, is another treatment of interest. If in response to these treatments, immunological diseases develop or become worse, immunologists take note. In a sense, these are experiments of nature – with a little nudge from the lab. Provided patients are interested in these treatments, immunologists and fertility specialists will try them, hope for pregnancy success, and observe whatever else happens. Lending credence to the view that immunological treatments are also experiments of nature is the fact that, even though the question of whether such treatments actually treat infertility has not been answered, they are offered anyway.[51] It has been suggested that paternal leucocyte immunization, for example, is no more effective than psychological support.[52] Ethics aside, if natural experiments are relied upon for data, patience will likely be required, as some autoimmune diseases may take decades to develop.

A second way in which experimental pathology is used to investigate pregnancy immunology is analogical: some immunologists think there are important similarities between pregnancy and both cancer and parasitism.[53] Fetal trophoblast cells are thought to resemble cancer cells insofar as they are proliferative and invasive.[54] And conversely, tumors are thought to 'mimic the natural situation of pregnancy; [human leucocyte] antigens are frequently not expressed in a normal manner, complement regulatory proteins are high and immunosuppressive conditions prevail'.[55] Alan Beer, of the Alan E. Beer Center for Reproductive Immunology and Genetics, offers an immunological test – the cost of which appears to start at approximately $3000 USD – for elevations of immune cells that purportedly mistake embryos for tumors. The website information for this test reads:

> Natural Killer (NK) cells are one of the oldest lymphocytes (white blood cells) in man. They have many functions. One of these functions is to produce a cytotoxic chemical called tumor necrosis factor (TNF). This is a chemotherapy drug that kills cancer cells in our body. In some couples, the embryo is misinterpreted as a cancer cell and when pregnancy is initiated, the Natural Killer cells of the woman increase in numbers and in killing power.[56]

What does it mean to misinterpret the embryo as a cancer cell? Or for that matter, a parasite? The parasitism analogy is based in part on the view that fetal nutrition comes at the expense of the mother. Gestational diabetes, for example, results from fetal mechanisms designed to increase glucose supply and this is seen by some as evidence

of an evolutionary history of maternal-fetal conflict over nutrition. The parasitism analogy is also based in part on the fact that fetuses go through stages, including a 'free-swimming' phase prior to 'invasion'. Some parasites go through a free-swimming phase prior to invasion too!

Obviously, there are relevant dissimilarities between pregnancy and cancer or parasitism. Analogies based on cancer and parasitism seem most germane when successful pregnancies are characterized as a result of an immunologically passive mother and fetuses are conceptualized as straightforwardly distinct. If one recognizes that maternal bodies actively construct the maternal-fetal interface, invasion ceases to be a relevant similarity. The fetus does not invade as cancer and parasites do. The analogy is further weakened by the blurry and gradual maternal-fetal interface: it is not clear that one distinct individual is invading another.

A third – and very commonplace – way in which pathology is used experimentally is in the use of immunodeficient mice as animal models. Though a very important experimental 'tool', results from immunodeficient mice can be difficult to interpret. This is mainly because redundancy is an important feature of the immune system. If one mechanism fails, others may compensate for the deficiency. For example, researchers can block production of certain cytokines in mice in order to investigate their functions – but other cytokines may compensate for those removed, making the results unclear.[57] *In vitro* isolations are always problematic in immunology for this reason. As immunologist David Clark says:

> The term 'hard science' has come to mean basic, rather than applied science, and to symbolize a fixation on the minutia of cells and molecules that may or may not have a direct relationship to phenomena in the real world. The speculation in which phenomenologists engaged in order to explain what they were seeing, in what way it was significant, and what they could do to alter events has been replaced by speculation concerning the meaning, significance, and (obvious) importance of molecules.[58]

It is difficult to interpret what the molecules are doing in contrived circumstances. Thus, experimental results obtained using immunodeficient mice always require biological contextualization.

Material practices involving women with fertility and immunological problems, and those based on analogies to cancer, parasitism, and immunodeficient mice, help to instantiate passivity and pathological reactivity as the primary forms of maternal reactivity. They also help to establish invasive foreignness as the principle property of the fetus. Thus, although a pathology framework can provide a useful starting point in the investigation of certain phenomena, it is important to keep its limitations in clear view. Experiments in reproductive immunology that are guided by the pathology framework exclude many kinds of immunological interactions and they can thus provide only a partial perspective on pregnancy immunology.

The Transplantation Framework

Medawar's term 'fetal semi-allograft' is commonly used in contemporary immunology and is based on a direct comparison between fetuses and transplanted organs (allografts).

Pregnancy is also sometimes referred to as 'natural transplantation' in immunological literature. For example:

> [a]lthough the rejection of surgically transplanted organs fits the self-nonself hypothesis, the theory in its most simple form does not explain the phenomenon of natural transplantation, namely pregnancy.[59]

Because the fetus expresses immunological markers from both the mother and father, only half – the paternal half – is immunologically nonself. Given this, it is curious that the term 'fetal semi-allograft' did not suggest a characterization of the maternal-fetal relationship along the lines of the relational model in philosophy: from an immunological perspective, the fetus is only partially maternal, after all. That it did not underscores the pervasive influence of the unitary immune self. The view that the fetus is foreign may also have been strengthened by Medawar's view that the maternal-fetal relationship in vertebrates is teleologically *inept*.[60]

The idea that the maternal-fetal relationship in vertebrates is teleologically inept may at first seem very strange. Pregnancy allows vertebrates to reproduce and thus enables the survival of species. It seems that pregnancy should be viewed as quite successful from a teleological standpoint. Two points may be helpful to explain, at least partially, why Medawar adopted this perspective on pregnancy. First, there are the dangers associated with pregnancy to consider, including immunological health problems, such as Rh disease, that affects mothers and their offspring. Second, Medawar viewed mother and fetus as distinct individuals with distinct evolutionary objectives. The mother's body will try to limit what she gives to the fetus, so as not to disadvantage herself. The fetus will try to get all it can in order to grow and develop. A conflict therefore exists in the relationship. The more independent they are of each other, then, the better off each might be. This claim might also seem very strange, but for Medawar, there was already evidence in the human fetal adrenal gland that the human fetus had evolved greater independence from the mother's physiology. The removal of the ovaries during pregnancy causes the loss of the pregnancy in some kinds of animals (mice, rabbits and cows), but not others (women, monkeys, mares and guinea-pigs).[61] In the latter group, the fetus has evolved large adrenals to secrete hormones necessary to the completion of pregnancy. The direction of this evolved change is, Medawar claims, 'unmistakable; it is towards a complete endocrinological self-sufficiency of the foetus and its membranes—in short, towards the evolution of a self-maintaining system enjoying the highest possible degree of independence of its environment'.[62] He continues: 'The human foetal adrenals stir up one's teleological predilections by their size alone, for although they rapidly undergo regression, the adrenals of the newborn infant are twenty times their relative adult size'.[63] Greater independence of the fetus is, for Medawar, a sign of evolutionary progress, for the fetus is no longer subject to the mother's biological inability to meet all of the needs of the fetus consistently and reliably. We should expect, then, to find a similar *immunological* independence via some protective boundary between mother and fetus: the better the boundary, the less risk posed to the fetus by the maternal immune system. For Medawar, viviparity

> raised for the first time in evolution the possibility that a mother might react immunologically upon her unborn children – might treat them as foreign bodies or as

> foreign grafts. The haemolytic disease that occurs in about one new-born child in 150 is an error of judgment of just this kind: it is, in effect, an immunological repudiation by the mother of her unborn child. Thus the existence of immunological reactions has not been fully reconciled with viviparity; and this is a blunder…[64]

And so, the foreignness of the fetus – what it has in common with an organ transplant – is emphasized, while any similarities of the fetus to the mother are seen as unproblematic and set to the margins of inquiry.

Like the pathology framework, the transplantation framework provides experimental models for research in reproductive immunology.[65] Experimental models of chimeras have been devised, such as the 'murine interspecies mating model', which involves transplantation of blastocysts from one mouse species, both with and without their own trophoblast, into mouse mothers of a different species.[66] This model has been used to study whether the trophoblast layer is a physical or immunological barrier. If the mother mouse is *Mus musculus* and the blastocyst is *M. caroli*, the blastocyst resorbs. If, however, a *musculus* trophoblast is used instead of the *caroli*'s own trophoblast, the *caroli* embryo will survive to term. This suggests to researchers that the trophoblast layer is an immunological barrier and thus fits the foreign-fetus model quite well. Fully xenogenic embryo transplants, such as between zebras and horses, have also been used as experimental models of pregnancy immunology.[67]

Some also think that microchimerism originating from pregnancy is more or less the equivalent of transplantation. This phenomenon, known of since the 1960s, occurs when cells from the mother or fetus enter the circulation of the other. Diana Bianchi, in trying to use this phenomenon to develop a method of prenatal diagnosis, found that fetal cells do not merely exist in pregnant women – they can persist, sometimes for decades, in women who have previously been pregnant. This discovery was initially thought 'so unexpected that despite her stellar reputation, colleagues first looked askance'.[68] Bianchi used Y chromosome fluorescent probes to find the presence of male fetal cells in the systems of women who had once been pregnant. Women with male children have been found to contain cells from those male children and similar results for women with daughters are inferred.[69] Microchimerism may thus be very common. In an editorial titled, 'So You Think Your Mother Is Always Looking Over Your Shoulder – She May be In Your Shoulder!' Judith Hall discusses recent studies showing that microchimerism occurs frequently.[70] Hall explains that if 'the cell is a stem cell, it may take up 'residency', produce daughter cells, and become a permanent part of the structures of that other person'.[71] Interestingly, Bianchi's experimental method uses biological sex as an experimental tool. Here, 'sex becomes scientifically performative, not as a pitfall or a blindspot, but as the most meaningful "experimental operator" to be tackled in particular research systems …'.[72] Thus, instead of marginalizing the issue of biological sex in immunology, Bianchi's procedure uses it to study microchimerism – and in so doing contravenes the idea that such exchanges are prohibited by a maternal-fetal barrier against immunological antagonism.

Understanding microchimerism as an instance of transplantation suggests this phenomenon is again one of self-nonself discrimination and the failure of the immune system to maintain maternal-fetal distinctness. There are, however, relevant disanalogies between fetuses and transplantation and between microchimerism and

transplantation. For starters, nothing is being 'transplanted' anywhere in pregnancy.[73] Organ transplants involve a surgical and immunological shock to the body; pregnancy does not. Further disruption is caused when 'mix and matching' between species, as in cases of xenotransplantation. The immune system, if it is about fixing damage, will behave differently under such circumstances. Organs also bring their own immune cells and biochemicals with them and, according to Matzinger's danger theory (discussed below), these may supply danger signals in the new host leading to transplant rejection. A related disanalogy is that organ transplants happen all at once, but embryos begin as single cells and gradually develop.[74] Thus, the transplantation analogy largely ignores the developmental aspect of pregnancy. Moreover, while immunological sameness works better for organ transplantation, immunological difference appears to work better for pregnancy.

The existence of relevant disanalogies between organ transplantation and pregnancy suggest there may be something fundamentally limited about experiments using chimeras and experiments that treat microchimerism as an instance of organ transplantation. The transplantation framework naturally leads us to think of the mother and fetus as self and nonself; that is, as two distinct beings separated by a boundary. It leads us to think of ways to get the mother to accept the fetus biologically by overcoming her immunological hostility to it. Pursuing the *partialness* of the 'semi-allograft' notion and its relation to a more beneficent maternal immune system may lead to immunological practices quite different from those of the organ transplantation framework. In adopting a relational model, which *can* accommodate partialness, different experimental practices may be developed – ones that either depend on analogies more relevant to pregnancy or are themselves entirely novel.

As the pathology and transplantation frameworks in reproductive immunology show, Medawar's warning that too much can be made of dangers to the fetus is advice worth listening to. The assumptions of maternal-fetal distinctness and antagonism structure experimentation in such a way that phenomena such as immunosuppression and organ transplantation take on more importance than they should. Loyalty to experimental systems that emphasize self-nonself discrimination may thus slow scientific understanding and explanation in this area. Most importantly, experiments modelled on pathology and transplantation may well miss experimental possibilities available to relational accounts of maternal-fetal immunity.

The Danger Model of Pregnancy Immunology

Viewed from the perspective of Matzinger's danger theory, the maternal-fetal immunological relationship most resembles Barbara Katz Rothman's body-part model of pregnancy. The danger model of pregnancy holds that the mother's immune system will not concern itself with the placenta-fetus unless it sends danger signals. The 'foreignness' of the fetus is thus irrelevant. If healthy, the placenta and fetus will be treated as any other part of the body. If unhealthy, an immune response to the fetus or placenta may occur, and the pregnancy may be lost. There is no need to maintain a barrier between mother and fetus or explain away contact between them. There is no paradox, and the maternal immune system need be neither inert nor inept. The danger model thus avoids

many of the problems generated by the sharply defined self characterized by self-nonself discrimination theory.

In addition to avoiding problems generated by self-nonself discrimination, the danger model opens space for new perspectives on immunological function in pregnancy and new experimental designs. For example, according to the danger model, some of the functions assigned immunological status in pregnancy may actually be *physiological*, not immunological, in nature.[75] Matzinger's danger model 'shifts control of immunity to the tissues that need protection rather than the [immune] cells that protect them'.[76] All tissues thus become immunological; but one might equally think of their activities as simply physiological. Immunologist Irun Cohen, though working with a different theoretical perspective, shares this emphasis on the physiological. For Cohen, specific immune reactions to pathogens are a smaller subset of ongoing immunological maintenance. Of this ongoing maintenance he says:

> We may define body maintenance as the implementation of processes critical to wound healing, tissue repair, angiogenesis, cell regeneration, and the disposal of abnormal cells and nonfunctional molecules. These processes, to a large degree, are triggered or performed by immune cells and by the molecular products of immune cells … Body maintenance, in short, depends on the immune activity that we call inflammation.[77]

How this physiological perspective affects experimentation is evident in the following example. Some reproductive immunologists propose that the enzyme indoleamine 2.3-dioxygenase (IDO) is responsible for suppressing the maternal immune system so as to prevent the rejection of the fetus.[78] Experimentally, it has been found that if the enzyme is inhibited in the placenta, fetal rejection results. This evidence seems to fit the foreign fetus model. Elizabeth Bonney and Polly Matzinger, however, argue that the enzyme's function may be *physiological*, not immunological, in nature. The enzyme IDO degrades tryptophan and one of the products of tryptophan is serotonin. That means that IDO will act in pregnancy to keep local levels of serotonin low. And this is exactly what is needed. Serotonin is a vasoconstrictor, but vasodilation is needed for a healthy pregnancy.[79] This result is particularly interesting given how convinced some are that experimental results show IDO prevents fetal rejection by turning off maternal T cells.[80] Bonney and Matzinger are not bound by the notion that a foreign fetus necessitates maternal immunosuppression, and so other explanations of these experimental results are more likely to arise.

Certainly, the disciplinary distinctions between physiology and immunology that I assume here are not uncontroversial. There are historical precedents for such controversies. In the early twentieth century, the study of anaphylaxis was increasingly split between physiologists and immunologists – and the widening gap was due to differences in experimental systems used in the respective scientific communities.[81] Similarly, one side of this recent split in pregnancy immunology invokes physiological understandings of immunology that are less concerned with self-nonself discrimination, and see immune function as tissue maintenance. On the other, self-nonself discrimination perspectives view highly specific immune reactions to foreign pathogens or entities as an example of immunological function *par excellence*. Here, immunology is about defence, not housekeeping. To adopt an experimental approach based on the danger model thus

involves not only a departure from self-nonself discrimination theory, but also a departure from perceived boundaries of immunology.

It is important to note that the danger model does not deny that immunological changes accompany pregnancy. The remission of certain autoimmune diseases and the increased vulnerability to certain infections during pregnancy make it clear that changes do occur. What is denied is that these changes hinge on identity. Identity does not serve as the primary organizing feature of maternal-fetal immunological relations. Thus, the troublesome assumptions of maternal-fetal distinctness, maternal passivity, and pathological reactivity simply drop out of the picture.

A Relational Model of Pregnancy Immunology

The question I would now like to consider is this: Does the danger model make enough room in its account of the maternal-fetal relationship for constructive maternal immunological activity? The answer is no, not quite. That the maternal immune system is indifferent to fetal identity in the danger model is somewhat problematic, for some recognition of fetal difference is probably necessary to conceive and maintain pregnancy. A more explicit hypothesis about beneficial maternal recognition of and response to the fetus is therefore important. The foreign-fetus model is of little help, for it links maternal recognition with the unary self and pathological reactivity. What is needed is a model based on a relational understanding of immune selfhood and reactivity. Here, a philosophical relational model is helpful. As Catriona Mackenzie explains,

> the experience of pregnancy, particularly in the early stages, is unique in the sense that it defies a sharp opposition between self and other, between inside and the outside of the body. From the perspective of the woman, there is no clear-cut boundary between herself and the foetus, between her body boundaries and the body boundaries of the foetus. The foetus, to the extent that it is experienced as part of the woman's body, is also experienced as part of her self, but as a part that is also other than herself.[82]

While Mackenzie here overgeneralizes the experience of pregnancy – many women do not experience the fetus this way – I wish to focus on her underlying ontological view about boundaries. The relational model of pregnancy immunology is similar in its view of boundaries insofar as there is *no clear-cut immunological boundary between mother and fetus*. Mother and fetus are not two unitary immune selves overshadowed by the threat of antagonism or invasion – but neither can they be collapsed into one unitary self. Rather, it seems that, at least in the ontological sense, both sameness and difference need to be taken into account.

Support for a relational model can be found in the fact that immunologists occasionally describe maternal-fetal immunological relations using terms that suggest positive, neutral, and non-antagonistic interactions. Terms such as maternal-fetal 'bi-directional traffic', 'dialogue', and fetal trophoblast 'migration' emphasize normal communication or at least neutral interaction.[83] Such terms contain the beginnings of a relational immunological model of maternal-fetal contact, though it does require some determination to draw this emerging model from papers in reproductive immunology. This is because there are no explicit theoretical models or experimental practices

built around beneficial relations. When beneficial relations present themselves in the laboratory they are still, for the most part, surprising.

The relational model is based on beneficial bi-directional immunological communication and makes constructive maternal reactivity a focal point of theory and practice. Empirical evidence suggests there are at least three kinds of communication that could support this emphasis on positive relationships. The first kind of beneficial communication involves HLA on fetal trophoblasts and may occur in a few different ways. First, an unusual form of HLA expressed by fetal trophoblasts (HLA-G) appears to be important for successful pregnancy.[84] This means that the mother's immune system recognizes fetal trophoblasts as being different from itself and that this recognition is beneficial – not harmful – to pregnancy. One reason these novel HLA antigens are expressed may be that they protect trophoblasts from attack by natural killer cells. Natural killer cells can attack cells that display no HLA or nonself markers. If trophoblast cells had no HLA antigens, natural killers could target them and the placenta would be harmed.[85]

A second way in which recognition occurs via human leucocyte antigens involves the degree of difference between paternal and maternal HLA. If the father's antigens are quite different from the mother's, there is a greater chance that a successful pregnancy will occur.[86] This is one rationale behind using paternal leucocyte immunization for women who have recurrent pregnancy loss.[87] Again, this suggests that recognition of fetal difference is beneficial to pregnancy. A third way recognition occurs via human leucocyte antigens should be strictly prohibited according to the foreign-fetus model. Despite the down-regulation of the usual major histocompatibility complex Class I genes and the expression of unusual HLA, the mother does encounter fetal cells expressing normal HLA at delivery, and probably before.[88] Whether this is beneficial or not is unclear. However, it appears that *unmediated* immunological contact can occur without causing rejection of the fetus.

A second kind of beneficial immunological communication is thought to help the placenta-fetus to develop properly. Here, the maternal immune system is actively involved in constructing the needed physical environment for pregnancy alongside fetal trophoblasts. For example, special uterine natural killer cells – a type of lymphocyte – appear to be involved in tissue remodelling at the maternal-placental interface.[89] These cells are thought to be involved in reconstruction of the uterine spiral arteries which ensure adequate blood flow between mother and fetus. One of the reasons bacterial vaginosis is thought causally relevant to pre-eclampsia is that preoccupation with infection prevents the maternal immune system from adequately constructing the maternal-fetal interface. Others contend that maternal immune responses to the placenta-fetus may have an important role in stimulating growth and differentiation of the maternal-fetal interface.[90] The orchestration of immunological cytokines is important here, for some inhibit growth and differentiation while others promote it.

A third kind of beneficial maternal-fetal immune communication involves microchimerism. Bianchi's research showing the exchange of cells between mothers and their fetuses is astonishing to some only because such exchanges were thought forbidden or pathological. What perhaps is unexpected is that microchimerism can bring positive benefits to mothers and their children. Bianchi found that some women have had their diseased organs repaired – sometimes almost wholly replaced – by cells

originating from their fetuses. Now that *is* astonishing; and a better candidate for 'natural transplantation' too. Studies also suggest that stem cells originating from mothers may participate in responses to infection and injury in their children.[91] This is not to say that microchimerism is always beneficial – it might also contribute to autoimmune disease in women. But the potential benefits of microchimerism are at least understandable within the context of the relational model, for the relational model does not require that maternal and fetal tissues be kept strictly distinct. In the local environment of pregnancy, the maternal-fetal interface consists of fetal and maternal cells that are in contact with each other. And while some of this contact is likely regulated, it is not possible to point to any particular dividing line between two individuals. The transition between mother, placenta, and fetus is gradual. Given this context, it is unsurprising that microchimerism occurs, and it is unsurprising that it has benefits.

Given the emerging evidence of beneficial communication, it is likely that immunological communication occurring between mothers and fetuses is crucial, not detrimental, to the success of pregnancy. Maternal awareness of the antigenic *semi*-difference of the fetus may well be key to the success of pregnancy. On this view, the exchange of immune cells and biochemicals between mother and fetus is routine and the relationship between them is beneficially interconnected and dynamic. Maternal-fetal interactions change as pregnancy proceeds and some stages may involve more immunological interaction than others. Most research papers in reproductive immunology still do not foreground beneficial maternal-fetal communication and the boundary diffusion between them. Some allude to benefits – they may note, for instance, that the maternal immune system helps fetal development – but, typically, the immunological paradox of pregnancy gets the introductory limelight. But as the benefits of immunological communication attest, pregnancy is not a paradoxical exception to the immunological rule; it challenges the rule itself.

Important to any relational model, then, should be the view that the maternal immune system behaves constructively in pregnancy; it is not simply a destructive force, kept at bay in circumstances of health. Experimental work taking the relational model to heart investigates the means by which maternal immune responses contribute to tissue remodelling and fetal development, as well as to the future health of offspring. Experiments taking a relational approach need not exclude pathological reactivity and maternal immunological indifference: pathology, indifference, and rejection of the fetus each describe certain maternal immunological activities. It is simply that in the relational model, bias towards unary selves and pathological reactivity is corrected, and the constructive immunological activities central to pregnancy are given the attention they are due.

Conclusion

I have argued that the foreign-fetus model is insufficient for understanding the maternal-fetal immunological relationship and that it inhibits further understanding. I have also argued that, despite its poor fit with pregnancy, the foreign-fetus model persists because of both its unexamined assumptions and its deep structuring of experimental practice. The foreign-fetus model forces permeable, blurry biological relationships into rigid conceptual containers. In so doing, it over-emphasizes difference. Its assumptions

operate implicitly in the experimental landscape and absorb attention that might instead be focused on more empirically adequate experimental models.

One available alternative to the foreign-fetus model is the danger model of pregnancy. Certainly, fresh new experimental approaches are suggested by it. However, the danger model, while making an important departure from the foreign-fetus model, does not do enough to emphasize positive maternal immunological reactivity. To some extent, it reduces the maternal-fetal relationship to one conceptual container – the mother's – and thereby under-emphasizes difference.

There is a need therefore to consider experimental frameworks wherein maternal immunology benefits fetuses and is studied without the conceptual overlay of rigid physical boundaries. The assumptions of distinctness and antagonism that are materially implicit in the pathology and transplantation experimental frameworks must be rendered explicit (and removed as needed) if the range of useful experimental models is to expand. A relational model of pregnancy immunology is an important place, conceptually speaking, to begin such an expansion. However, the development of a relational-style model may require that more research in reproductive immunology be conducted outside of infertility clinics, cancer treatment centres and transplantation centres. These environments help perpetuate the pathology and transplantation experimental frameworks – as well as the focus on achieving pregnancy and successful organ transplantation over the improvement of women's immunological health.

The marginalization of women in medical research generally does impact our knowledge of the immunology of pregnancy and the immunological health of women. Hypotheses about maternal antagonism are rooted in and strengthened by problematic medical and social assumptions about mothers and fetuses, assumptions which are themselves partially responsible for the marginalization of certain features of women's biology in research – such as those features where there is active maternal involvement. Research framed by a genuine interest in the immunology of women – that is, an immunology wherein females defend themselves against infection and autoimmune disease and can do so whilst constructing healthy pregnancies – should look very different from research focused on the minutiae of molecular self-nonself discrimination between mother and fetus.

I conclude with the general observation that there remains a need for feminist critiques of science, especially ones that engage experimental practice. Even when problematic theoretical assumptions are identified, uprooted and rejected, their experimental counterparts may persist. As the methods of the pathology and transplantation frameworks in this case demonstrate, procedures, practical models, tools, digitization and data may all perpetuate particular ways of conceptualizing immune function. Destabilizing problematic experimental approaches is therefore vital to the advancement of immunological research concerning women and their pregnancies.

Notes

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2 Ole Christiansen, quoted in M. Hutchinson, 'Miscarriage Risk Grows After Boy Babies', *BBC News* <http:// news.bbc.co.uk> accessed 2 July 2003; see also 'The Sweet Smell of the Immune System', *Nature Science Update* <http://www.nature.com/nsu/> accessed 7 March 2001.

3 Kelton Tremellen, quoted in Helen Pearson, 'Immunity's Pregnant Pause', *Nature Science Update*, 21 November 2002, pp. 265–6 at p. 265.

4 Gina Kolata, 'The Heart's Desire', *The New York Times,* 11 May 2004 <http://query.nytimes.com/gst/fullpage.html?sec=health&res=980CE0D8123CF932A25756C0A9629C8B63> accessed 10 November 2006.

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6 Caleb Kallen and Aydin Arici, 'Immune Testing in Fertility Practice: Truth or Deception?', *Current Opinion in Obstetrics and Gynecology*, **15**, 2003, pp. 225–31.

7 Ibid.

8 Tetsuji Tanaka, Naohiko Umesaki, Junko Nishio, Kyoko Maeda, Tomoyuki Kawamura, Nobuo Araki *et al.*, 'Neonatal thrombocytopenia induced by maternal anti-HLA antibodies: a potential side effect of allogenic leukocyte immunization for unexplained recurrent aborters', *Journal of Reproductive Immunology*, **46**, 2000, pp. 51–7; Patrizia Casoli, Bruno Tuniati and Giovanni La Sala, 'Fatal Exacerbation of Systemic Lupus Erythematosus After Induction of Ovulation', *Journal of Rheumatology*, **24**, 1997, pp. 1639–40; Avraham Ben-Chetrit and Eldad Ben-Chetrit, 'Systemic Lupus Erythematosus Induced By Ovulation Induction Treatment', *Arthritis and Rheumatism*, **37**, 1994, pp. 1614–17; J. Bux, E. Westphal, F. de Sousa, G. Mueller-Eckhardt, C. Mueller-Eckhardt, 'Alloimmune neonatal neutropenia is a potential side effect of immunization with leukocytes in women with recurrent spontaneous abortions', *Journal of Reproductive Immunology*, **22**, 1992, pp. 299–302; Ian Katz, Benjamin Fisch, Shoshana Amit, Jardena Ovadia, and Yona Tadir, 'Cutaneous Graft-Versus-Host-Like Reaction After Paternal Lymphocyte Immunization for Prevention of Recurrent Abortion', *Fertility and Sterility*, **57**, 1992, pp. 927–9.

9 Caroline Whitacre, 'Sex Differences in Autoimmune Disease', *Nature Immunology*, **2**, 2001, p. 777–80; Denise Jacobson, Stephen Gange, Noel Rose, and Neil Graham, 'Epidemiology and Estimated Population Burden of Selected Autoimmune Diseases in the United States', *Clinical Immunology and Immunopathology*, **84**, 1997, pp. 223–43.

10 George Annas and Laura Purdy discuss this model in their respective philosophical analyses of women as 'fetal containers'. See George Annas, 'Pregnant Women as Fetal Containers', *Hastings Center Report*, **16**, 1986, pp. 3–14; Laura Purdy, 'Are Pregnant Women Fetal Containers?', *Bioethics*, **4**, 1990, pp. 273–91.

11 Barbara Katz Rothman, *Recreating Motherhood: Ideology and Technology in a Patriarchal Society*, New York: Norton, 1989.

12 Isabel Karpin, 'Legislating the Female Body: Reproductive Technology and the Reconstructed Woman', *Columbia Journal of Gender and Law*, **3**, 1992, pp. 325–33.

13 Deborah Hornstra, 'A Realistic Approach to Maternal-Fetal Conflict', *Hastings Center Report*, **28**, 1998, pp. 7–12.

14 Polly Matzinger, 'Tolerance, Danger, and the Extended Family', *Annual Review of Immunology*, **12**, 1994, pp. 991–1045.

15 Interestingly, we do not need a clear biological or ontological separation between maternal and fetal selves to justify the psychological experience of the fetus as a foreign invader. Though I will argue that the view that the fetus is tumor-like creates problems for research, the fetus can be viewed from a psychological standpoint as tumor-like: while neither clearly self nor nonself, the fetus (like a tumor) may be something one strongly desires to be rid of.

16 With respect to the importance of experimental practice to feminist studies of science see Sharyn Clough *Beyond Epistemology: A Pragmatist Approach to Feminist Science Studies*, Lanham: Rowan and Littlefield Publishers, Inc., 2003.

17 Moira Howes, 'The Self of Philosophy and the Self of Immunology', *Perspectives in Biology and Medicine*, **42**, 1998, pp. 118–30.

18 Donna Haraway, 'The Biopolitics of Postmodern Bodies: Determinations of Self in Immune System Discourse', *Differences*, **1**, 1989, pp. 3–43; Emily Martin, *Flexible Bodies: Tracking Immunity in American Culture from the Days of Polio to the Age of AIDS*, Boston: Beacon Press, 1994; Lisa Weasel, 'Dismantling the Self/Other Dichotomy in Science: Towards a Feminist Model of the Immune System', *Hypatia*, **16**, 2001, pp. 27–44.

19 Leslie Brent, 'Tolerance Revisited' in Moulin and Cambrosio (eds) *Singular Selves,* 2001 (n. 5), pp. 44–52.

20 Peter Medawar, *The Uniqueness of the Individual*, London: Methuen and Co. Ltd., 1957, p. 181.

21 Ibid.

22 Medawar, 'Some immunological and endocrinological problems', 1953 (n. 1).

23 Medawar thinks that the 'vascular quarantine' around the placenta-fetus establishes the uterus as an immunologically privileged site, like the brain. The vascular quarantine would, he supposes, prevent large particles like cells and bacteria from travelling across the maternal-placental interface and would thus protect against infection as well as maternal immunological rejection.

24 Of course, so characterized, this immunosuppression makes little evolutionary sense.

25 Medawar, *The Uniqueness of the Individual,* 1957 (n. 20), pp. 181–2

26 Ibid., p. 124. Medawar is also aware that cancer cells could be transmitted to the fetus.

27 Joan S. Hunt (ed.), *HLA and the Maternal-Fetal Relationship*, Austin, TX: R.G. Landes Company, 1996, Preface.

28 Ibid.

29 The fetal trophoblast originates from the outer layer of the morula and goes on to develop the placenta. The embryo forms from the inner cells of the morula.

30 Carole Ober and Katrin van der Ven, 'HLA and Fertility', in Hunt (ed.), *HLA and the Maternal-Fetal Relationship*, 1996 (n. 27), pp. 148–9.

31 In the Fas-Fas ligand system, for example, trophoblast cells having the Fas ligand initiate the dying process in immune cells containing the Fas protein. The Fas-Fas ligand system, then, may decrease the numbers of T cells specific for fetal antigens present at the maternal-fetal interface. See Gil Mor, L.S. Gutierrez, M. Eliza, F. Kahyaoglu and A. Arici, 'Fas-Fas ligand system-induced apoptosis in human placenta and gestational trophoblastic disease', *American Journal of Reproductive Immunology*, **40,** 1998, pp. 89–94.

32 Ashley Moffett-King, 'Natural Killer Cells and Pregnancy', *Nature Reviews Immunology*, **2**, 2002, pp. 656–63.

33 Cytokines are proteins involved in cell signalling between immune cells and cells of the body. They include interferons, interleukins, colony stimulating factors, tumour necrosis factors and

transforming growth factors. Th1 (T-helper lymphocytes) and Th2 (T-helper 2 lymphocytes) each produce different profiles of cytokines.

34 Tom Wegmann, G.H. Lin, L. Guilbert, and T.R. Mossman, 'Bi-directional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a Th2 phenomenon?', *Immunology Today*, **14,** 1993, pp. 353–6. Support for the Th2 bias model can be found, for example, in David A. Clark, 'Signaling at the Fetomaternal Interface', *American Journal of Reproductive Immunology*, **41**, 1999, pp. 169–73; and N. Gleicher, 'Some Thoughts on the Reproductive Autoimmune Failure Syndrome (RAFS) and Th-1 Versus Th-2 Immune Responses', *American Journal of Reproductive Immunology*, **48**, 2002, p. 252–4. Others suggest the evidence may be merely correlational. See, for example, Anne Croy, 'Where now for the Th1/Th2 paradigm of the gestational uterus?', *Journal of Reproductive Immunology*, **51**, 2000, pp. 1–2; V. Geenen, S. Perrier de Hautervive, M. Puit, A. Hazout, F. Goffin, F. Frankenne, M. Moutschen, J.M. Foidart, 'Autoimmunity and Pregnancy: Theory and Practice', *Acta Clinica Belgica*, **57**, 2002, pp. 317–24; and L. Svensson, M. Avrola, M. Sällström, R. Holmdahl, and R. Mattsson, 'The Th2 cytokines IL-4 and IL-10 are not crucial for the completion of allogenic pregnancy in mice', *Journal of Reproductive Immunology*, **51**, 2001, pp. 3–7.

35 A.L. Veenstra van Nieuwenhoven, M.J. Heineman, and M.M. Faas, 'The Immunology of Successful Pregnancy', *Human Reproduction Update*, **9**, 2003, pp. 347–57.

36 Charles Janeway, 'The Immune System Evolved to Discriminate Infectious Nonself from Noninfectious Self', *Immunology Today*, **13**, 1992, pp. 11–16; J. Kurtz, 'Memory in the innate and adaptive immune systems', *Microbes and Infection*, **6**, 2004, pp. 1410–17; Polly Matzinger, 'The Danger Model: A Renewed Sense of Self', *Science*, **296**, 2002, pp. 301–5; Tina Rich, *Toll and Toll-Like Receptors: An Immunologic Perspective*, New York: Kluwer Academic/Plenum Publishers, 2005.

37 Mark Jackson, *Allergy: The Making of Modern Malady*, London, Reaktion Books, 2006, pp. 62–4; idem, 'Allergy: The Making of a Modern Plague', *Clinical and Experimental Allergy*, **31**, 2001, pp. 1665–71.

38 Jackson, *Allergy,* 2006 (n. 37).

39 Ohad Parnes, '"Trouble from within": Allergy, Autoimmunity, and the Pathology in the First Half of the Twentieth Century', *Studies in History and Philosophy of Biological and Biomedical Sciences*, **34**, 2003, pp. 425–54.

40 Invasion terminology is used extensively in reproductive immunology. Statements such as the following are typical: 'Since the invading trophoblast represents a semi-allograft, it should be rejected by the mother': V. Abrahams, S. Straszewski-Chavez, S. Guller and G. Mor, 'First trimester trophoblast cells secrete Fas ligand which induces immune cell apoptosis', *Molecular Human Reproduction*, **10**, 2004, pp. 55–63.

41 The difficulties with the term 'hostile' are obvious. The difficulties with the term 'mucus' are perhaps less frequently discussed. Cervical 'mucus' is problematic because cervical products are less analogous to mucus than they are, perhaps, to seminal *fluids*. Thus, 'cervical fluid' is a better term.

42 P.Y. Robillard, G.A. Dekker, and T.C. Hulsey, 'Evolutionary Adaptations to Pre-eclampsia/Eclampsia in Humans: Low Fecundability Rate, Loss of Oestrus, Prohibitions of Incest and Systematic Polyandry', *American Journal of Reproductive Immunology*, **47**, 2002, pp. 104–11.

43 Clark, 'Signaling at the Fetomaternal Interface' (n. 34).

44 D.A. Viniker, 'Hypothesis on the role of sub-clinical bacteria of the endometrium (bacteria endometrialis) in gynaecological and obstetric enigmas', *Human Reproduction Update*, **5**, 1999, pp. 373–85.
45 Hans-Jörg Rheinberger, *Toward a History of Epistemic Things: Synthesizing Proteins in the Test Tube*, Stanford: Stanford University Press, 1997.
46 Ibid.; see also Ian Hacking, 'The Self-Vindication of the Laboratory Sciences', in Andrew Pickering (ed.), *Science as Practice and Culture*, Chicago: Chicago University Press, 1992, pp. 29–64.
47 Hacking, 'The Self-Vindication of the Laboratory Sciences' (n. 46).
48 Peter Galison, *How Experiments End*, Chicago: University of Chicago Press, 1987.
49 Rheinberger, *Toward a History of Epistemic Things* (n. 45), p. 27.
50 M. Baines and R. Gendron, 'Natural and Experimental Animal Models of Reproductive Failure', in Gérard Chaouat (ed.), *Immunology of Pregnancy*, Boca Raton, FL: CRC Press, Inc., 1993, pp. 173–203.
51 R. Ramhorst, E. Agriello, S. Zittermann, M. Pando, J. Larriba, M. Irigoyen, M. Cortelezzi, L. Auge, E. Lombardi, J.J. Etchpareborda, C. Contreras Ortiz, L. Fainboim, 'Is the Paternal Mononuclear Cells' Immunization a Successful Treatment for Recurrent Spontaneous Abortion?', *American Journal of Reproductive Immunology*, **44**, 2000, pp. 129–35.
52 Daniel Wallace, Maurice Druzin, and Robert Lahita, 'Clinical Rheumatologic Applications of Reproductive Immunology', *Arthritis and Rheumatism*, **40**, 1997, pp. 209–16.
53 David Clark *et al*. gives an overview of the tumor and parasitism models and some of the problems with them. See David Clark, P.C. Arck and Gérard Chaouat, 'Why did your mother reject you? Immunogenetic Determinants of the Response to Environmental Selective Pressure Expressed at the Uterine Level', *American Journal of Reproductive Immunology*, **41**, 1999, pp. 5–22.
54 V.I. Govallo, *The Immunology of Pregnancy and Cancer*, Commack, NY: Nova Science Publishers, 1993.
55 Joan Hunt and H. Hutter, 'Current Theories on Protection of the Fetal Semiallograft', in Hunt (ed.), *HLA and the Maternal-Fetal Relationship* (n. 27), p. 43.
56 <http://repro-med.net/tests/nkassay.php> accessed 24 August 2006. This is an interesting website, particularly given the patchy evidence for the effectiveness of immunological tests and treatments and the lack of standardization.
57 See, for example, Svensson *et al*., 'The Th2 Cytokines' (n. 34)
58 David Clark, 'Hard Science Versus Phenomenology in Reproductive Immunology', *Critical Reviews in Immunology*, **19**, 1999, pp. 509–39 at p. 510. For Clark, the term 'phenomenology' appears to refer to clinical observations that are not supported by knowledge of the underlying mechanisms (p. 509).
59 Gary Entrican, 'Immune Regulation during Pregnancy and Host-Pathogen Interactions in Infectious Abortion', *Journal of Comparative Pathology*, **126**, 2002, pp. 79–94 at p. 79.
60 Medawar, 'Some immunological and endocrinological problems' (n. 1).
61 Ibid., p. 322.
62 Ibid., p. 324.
63 Ibid., p. 333.
64 Peter Medawar, *The Future of Man*, London: Methuen and Co. Ltd., 1959, p. 101.
65 Ober and van der Ven, 'HLA and Fertility' (n. 30), p. 133.
66 Baines and Gendron, 'Natural and Experimental Animal Models' (n. 50), p. 183.

67 W.R. Allen, J.H. Kydd, and D.F. Antczack, 'Successful Application of Immunotherapy to a model of pregnancy failure in equids' in D.A. Clark and B.A. Croy (eds), *Reproductive Immunology*, Elsevier: Amsterdam, 1986, pp. 253–61; Gérard Chaouat, 'The Roots of the Problem: "The Fetal Allograft"', in Chaouat (ed.), *Immunology of Pregnancy* (n. 50), pp. 1–17.

68 Gina Kolata, 'Promise, in Search of Results; Stem Cell Science Gets Limelight; Now it Needs a Cure', <http://nytimes.com> accessed 24 August 2004.

69 Interestingly, some women without male children have been found to contain male microchimeric cells. Researchers think this may be due to pregnancies that were lost.

70 Judith Hall, 'So You think Your Mother is Always Looking Over Your Shoulder? – She May Be *In* Your Shoulder!', *The Journal of Pediatrics*, **142**, 2003, pp. 233–4.

71 Ibid., p. 233.

72 Cynthia Kraus, 'Naked Sex in Exile: On the Paradox of the "Sex Question" in Feminism and in Science', *NWSA Journal*, **12,** 2000, p. 160.

73 Chaouat, 'The Roots of the Problem' (n. 67), p. 2.

74 Ibid.

75 Elizabeth Bonney and Polly Matzinger, 'The Maternal Immune System's Interaction with Circulating Fetal Cells', *Journal of Immunology*, **158**, 1997, pp. 40–7.

76 Colin Anderson and Polly Matzinger, 'Danger: The View From the Bottom of the Cliff', *Seminars in Immunology*, **12**, 2000, pp. 231–8 at p. 232.

77 Irun Cohen, 'Discrimination and Dialogue in the Immune System', *Seminars in Immunology*, **12**, 2000, pp. 215–19 at p. 215.

78 D.H. Munn, M. Zhou, J.T. Attwood, I. Bondarev, S.J. Conway, B. Marshall, C. Brown and A.L. Mellor, 'Prevention of allogenic fetal rejection by tryptophan catabolism', *Science*, **281**, 1998, pp. 1191–3.

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81 Ilana Löwy, 'On Guinea Pigs, Dogs and Men: Anaphylaxis and the Study of Biological Individuality, 1902–1939', *Studies in History and Philosophy of Biological and Biomedical Sciences*, **34**, 2003, pp. 399–423.

82 Catriona Mackenzie, 'Abortion and Embodiment', *Australian Journal of Philosophy*, **70**, 1992, pp. 136–55 at p. 148.

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84 Ober and van der Ven, 'HLA and Fertility' (n. 30).

85 Entrican, 'Immune Regulation' (n. 59), p. 82.

86 Ober and van der Ven, 'HLA and Fertility' (n. 30); Chaouat, 'The Roots of the Problem' (n. 67).

87 Hunt, *HLA and the Maternal-Fetal Relationship* (n. 27), Preface.

88 It is suggested that in such cases, harmful maternal immune reactions to paternal HLA may be avoided because trophoblast cells contain very high levels of a protein that interferes with the complement cascade (Hunt and Hutter, 'Current Theories' [n. 55], p. 39).

89 Moffett-King, 'Natural Killer Cells' (n. 32).

90 Van Nieuwenhoven *et al.*, 'The Immunology of Successful Pregnancy' (n. 35); H. Adachi, K. Takakuwa, T. Mitsui, K. Ishii, M. Tamura, and K. Tanaka, 'Results of Immunotherapy for Patients with Unexplained Secondary Recurrent Abortions', *Clinical Immunology*, **106**, 2003, pp. 175–80; Joan Hunt and M. Soares, 'Features of the Maternal-Fetal Interface', in Hunt (ed.), *HLA and the Maternal-Fetal Relationship* (n. 27), pp. 1–26.

91 Hall, 'So You think Your Mother is Always Looking Over Your Shoulder?' (n. 70), p. 234; Nelson, 'Microchimerism' (n. 83); Diana Bianchi, 'Fetomaternal cell trafficking: a new cause of disease?', *American Journal of Medical Genetics*, **91**, 2000, pp. 22–8. Microchimerism may aid recipients of organ transplantation in a similar way by helping them develop tolerance to the new organ. See Thomas E. Starzl, Anthony J. Demetris, Massimo Trucco *et al.*, 'Chimerism after Liver Transplantation for Type IV Glycogen Storage Disease and Type 1 Gaucher's Disease', *The New England Journal of Medicine*, **328**, 1993, pp. 745–9; and A.W. Thomson, L. Lu, N. Murase, A.J. Demetris, A.S. Rao, and T.E. Starzl, 'Microchimerism, dendritic cell progenitors and transplantation tolerance', *Stem Cells*, **13,** 1995, pp. 622–39).

CHAPTER THIRTEEN

Canadian Vaccine Research, Production and International Regulation: Connaught Laboratories and Smallpox Vaccines, 1962–1980

Christopher J. Rutty

In the more than two centuries since Edward Jenner identified the effectiveness of vaccine lymph to protect against smallpox, the success of a wide variety of vaccines has demonstrated the power of the human immune system, when precisely stimulated, to protect against the most deadly or debilitating infectious diseases. The development of the immunological science behind the effectiveness of various vaccines has been the focus of some historical attention, as has, to varying degrees, their evaluation, standardization, regulation, delivery and application.[1] However, considerably less historical attention has been focused on the scientific and practical development and large-scale production and quality control of vaccines. This is primarily because of limits placed upon direct access to primary records generated by vaccine manufacturers, most of which, especially in North America, are large private companies that generally do not welcome academic historians into their archival collections – assuming any records have been retained in the first place.

In Canada, there has been one primary producer of vaccines and other public health biological products for most of the twentieth century. Known variously as Connaught Antitoxin Laboratories, Connaught Laboratories and Connaught Medical Research Laboratories while a self-supporting, non-profit part of the University of Toronto from 1914 through 1972,[2] a large and valuable collection of primary records from this period and later have been preserved at what is now the Connaught Campus of Sanofi Pasteur Limited in Toronto.[3]

From 1916 through 1980, and especially after 1962, Connaught Laboratories produced glycerinated and then freeze-dried smallpox vaccines that simultaneously met the increasingly rigorous regulatory standards of Canada, the United States, and the World Health Organization. Indeed, Connaught was a key player in establishing such international standards and it was one of, if not the only, smallpox vaccine producer in the world that had to regularly meet and exceed such domestic and international standards.[4] Satisfying domestic vaccine demands and maximizing profits were the main focus of commercial vaccine producers, particularly in the US. Without the need to satisfy private shareholders, and with a broader, more academic approach to global public health, Connaught developed a tradition of stronger and more open international

connections with governments, regulators, public health organizations like the WHO, as well as other vaccine producers. Moreover, Canadian export regulations allowed Connaught to more easily export vaccines than US manufacturers; Connaught only had to satisfy the regulatory requirements of the importing country, while US commercial producers first had to meet American standards. During the early 1960s, this situation gave Connaught an important advantage, particularly during the early development of Sabin oral polio vaccine (1960–62) as the Labs could export the still experimental vaccine to countries facing major polio epidemics before it was licensed in Canada or the US. Cold war politics and Canadian neutrality also tended to favour Connaught over US and Soviet vaccine producers during this period.[5] Nevertheless, Connaught had always worked closely with American regulators at the National Institutes of Health to ensure their vaccines and other biologicals met US standards to allow for export south of the border, while also working to meet increasingly rigorous Canadian regulatory standards, which were generally based on American standards, but sometimes diverged from them, as was the case with smallpox vaccine. In 1967, Connaught's international reputation and experience with smallpox vaccines were recognized when the WHO designated it one of two Regional Smallpox Vaccine Reference Laboratories, responsible for working with local smallpox vaccine producers in the Western Hemisphere to improve standards and provide testing and consultation services. The National Institute of Public Health in Bilthoven, Netherlands, provided similar services for the Eastern Hemisphere.

Within this context, Dr Paul Fenje oversaw Connaught's smallpox vaccine program from 1962 through 1979, quietly and effectively raising standards, driven by pressures from national and international regulators, academic and commercial interests, and a growing determination to ultimately eradicate 'the speckled monster' from the planet.[6]

The sudden emergence of smallpox after 9/11 as a potential bio-terrorist weapon focused considerable energy on expediting the preparation of renewed supplies of smallpox vaccines around the world.[7] A new Canadian vaccine stockpile has been produced from a series of Vaccinia pulps originally prepared at Connaught in 1979 and then, fortunately, preserved in a deep freeze after smallpox was declared eradicated and vaccine production shut down. Not unlike the frozen Vaccinia pulps, the unique archival record of Connaught's smallpox vaccine development and production activities preserved at the Connaught Campus opens an otherwise closed window on the practical and dynamic world of vaccine development and manufacturing during the twentieth century.

This paper builds upon an earlier article that described Connaught's broader contributions to the global smallpox eradication effort.[8] The main focus here will be on Fenje's smallpox vaccine development and production work and an examination of the scientific and practical advantages and constraints he faced in raising international smallpox vaccine standards, and then consistently meeting and exceeding them in supplying the World Health Organization's smallpox eradication program with what he and others, metaphorically, though not inaccurately, characterized as 'the best dried smallpox vaccine ever made in this galaxy'.[9]

Prelude: Smallpox Vaccination in Canada: The Pre-Modern Era, 1797–1916

Several authors, including Jennifer Keelan in this volume of essays (and in her dissertation), have described and analyzed the pre-modern era of smallpox vaccination,

including the Canadian context.[10] However, the primary focus of this scholarship has been more on the various intersections between vaccination theories, the empirical assessment of its efficacy and political debates surrounding the use and value of the vaccine than on the practical aspects of its production on the various vaccine farms.

The first steps towards more potent and pure smallpox vaccine supplies began with the promotion of a new means of propagating vaccine, which used only 'pure bovine vaccination'. This new approach to selecting and producing good stock vaccine lymph distinguished itself from the mélange of techniques and vaccine lymphs in use. Pure bovine vaccine was made using only spontaneous cowpox as a seed vaccine material, and was propagated in a series solely in the cow. Other more popular means of vaccine production involved a variety of starter materials, which had been propagated serially through a variety of hosts, including humans (see Keelan this volume). The most important improvement in smallpox vaccine production came in 1891 when glycerin was first used to dilute lymph. Not only did glycerin allow for vaccine production on a larger scale, it was also a preservative of the virus, and destroyed extraneous bacteria. The vaccine could now be more easily tested in the laboratory, although there were efforts to systematically test lymphs in the lab much earlier (see Keelan and Rusnock this volume). Sterile glass capillary tubes were also introduced at the same time in which the glycerinated vaccine was packaged and distributed. Other antiseptics, including phenol, were later used to ensure purity in vaccine production.[11]

Smallpox vaccine stations overseen by interested physicians and local health boards and supplied with vaccine imported from the United States, or a local supply, facilitated the distribution of smallpox vaccine in Canada through the mid-1880s.[12] In addition, with support from the Montreal Board of Health, the 'Montreal Cow-pox Institute' was established in 1878. Larger scale production began on a commercial and government-sponsored basis after the great 1885 Montreal smallpox epidemic. L'Institut vaccinogène de Québec was established in 1886 in Sainte-Foy, just outside Quebec City and operated with the support of the Quebec provincial government, while in 1899, l'Institut vaccinol de Montréal, a privately funded company, was established in Montreal, although it received some support from the city.[13]

The first smallpox vaccine supply in Ontario commenced in 1885 when the Ontario Vaccine Farm was established in Palmerston. Influenced by the 1885 Montreal epidemic, as well as by a serious smallpox outbreak north of Belleville in 1884, the Provincial Board of Health sponsored the Palmerston Vaccine Farm. Managed single-handedly by Dr Alexander Stewart, and after his death in 1911 by Dr Herbert Coleman, the Ontario Vaccine Farm produced Vaccinia points, despite increasing imports of higher quality glycerinated vaccine, until 1916.[14]

Connaught Laboratories and Smallpox Vaccine, 1916–1962

Prompted by growing domestic, and particularly military, demand for higher quality, glycerinated smallpox vaccine, in 1916 the Antitoxin Laboratories of the University of Toronto purchased the calves and equipment of the Ontario Vaccine Farm.[15] The Antitoxin Laboratories were founded in 1913 in a small backyard stable in west Toronto by Dr John G. FitzGerald to provide life-saving public health products in Canada, such as diphtheria and tetanus antitoxins, at a price that was within the reach of everyone.

Figure 13.1 Connaught Laboratories' first smallpox vaccine production facility was located in several isolated rooms at the south-east corner of this building (the front corner at the left end of the image). Main laboratory building, c. 1917-18, Connaught Antitoxin Laboratories, Farm Section, University of Toronto. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, Acc1180.

Figure 13.2 After packaging bulk smallpox vaccine imported from the New York City Health Department Laboratories for about a year, Connaught Laboratories began to fully prepare its own smallpox vaccine in September 1917. The first step in the production process was shaving and preparing the calf for inoculation. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, Acc1954.

Encouraged by his efforts and enthusiasm, and initial antitoxin sales to the Ontario government, on 1 May 1914, the University of Toronto officially established the Antitoxin Laboratories in the basement of the Medical Building.[16]

A severe shortage of tetanus antitoxin during the first year of World War I prompted the donation by Colonel Albert E. Gooderham (Ontario Red Cross Chairman and a University of Toronto Governor) of a large farm property 17 kilometers north of the University campus, along with new laboratory facilities for expanded antitoxin production. In early 1916 these new buildings were almost completed and a corner section of the main laboratory building was renovated for smallpox vaccine production, accommodated and isolated in four separate rooms with an outside entrance.

In the meantime, as was the case when production of diphtheria and tetanus antitoxins was initiated in Toronto in 1914–15, bulk supplies of smallpox vaccine, along with scientific and technical assistance, was sought from the New York City Health Department's Laboratories. FitzGerald had developed a close relationship with its Director, Dr William H. Park, beginning with his post-graduate studies there in 1910, and was able to negotiate an arrangement for supplies and testing of antitoxins and vaccines at cost. For example, during September and October 1915, a total of 19,760 points of smallpox vaccine were supplied from New York City, the first shipment of 7,500 points immediately forwarded from Toronto to Winnipeg (2,500 points) and Niagara (5,000 points).[17]

The first batch of smallpox vaccine fully produced in the lab in Toronto was harvested from Calf #1 on 12 September 1917, shortly before the official opening of the 'Connaught Antitoxin Laboratories and University Farm'. Connaught's opening took place on 25 October 1917 and was christened by Gooderham after the Duke of Connaught, Canada's Governor General during WWI, and first patron of the Canadian Public Health Association. With the vaccination of the calves and harvesting of the vaccine managed by Albert Double, and after several tests carried out by Frank Scruby, particularly for streptococcus, tetanus and anaerobic bacteria, proved negative and clinical tests showed 'good takes', Connaught's first lot of 6,000 capillary tubes of smallpox vaccine was released on 21 December 1917.[18]

Connaught's smallpox vaccine production then rose sharply under the leadership of the lab's Assistant Director, Dr Robert D. Defries.[19] Defries, Hilda Finegan (secretary, purchasing agent, shipper) and Leila Hanna (laboratory assistant), made several trips to the United States to secure not only an original Vaccinia calf seed virus supply from the New York City Health Department – which, Defries thought was '…an original cowpox strain from England', first brought to New York in the 1850s[20] – but also all the components for smallpox vaccine packaging, including capillary tubes, scarifying needles and rubber bulbs.[21] The greatest demand for smallpox vaccine came from the Canadian military, which had purchased more than 600,000 capillary tubes from Connaught by the end of the war. A large quantity of vaccine was also prepared for provincial health departments and others across Canada, including hospitals and individual physicians.[22]

Not long after the end of the war, domestic demand for Connaught's smallpox vaccine grew sharply when a series of localized smallpox outbreaks struck parts of central Ontario. The Toronto area was struck in 1919 and 1920, and then Ottawa in 1921. A total of 3,046 cases were reported in 1919 in the province, and another 5,129 cases and

33 deaths in 1920. As FitzGerald noted in his Annual Report, 'There was, as a result, an enormous demand for smallpox vaccine and the resources of the Laboratories were greatly strained to meet the need'. Moreover, 'The output of vaccine for each of the months during which the epidemic continued was almost as great as the production for any previous year since the opening of the Laboratories'. In total, sufficient vaccine for 489,270 vaccinations was produced during October 1919 through January 1920, and another 500,000 in 1921.[23]

This level of smallpox vaccine production provided a valuable opportunity for Connaught scientists not only to build up practical experience with vaccine production, but also to study the effectiveness of the vaccine, investigate complications, and to focus on improving its quality. In particular, occasional complaints of vaccine failures from doctors, particularly during the Ontario smallpox epidemic in 1919–20, underscored the importance of how the vaccine was being shipped, stored and administered, and especially how heat could easily destroy its potency. Such complaints also highlighted the limited understanding of vaccination and vaccines among some physicians during this period and the importance of Connaught keeping detailed production records so that individual

Figure 13.3 During the last years of World War I and expanding into the 1920s, Connaught Laboratories supplied smallpox vaccine, among other vaccines and antitoxins, to all provinces in Canada, as well as to other parts of the British Empire. This promotional map, dating from about 1920-21, was displayed at such public events as the Canadian National Exhibition and highlighted Connaught's mission: 'Established for research investigation in Preventive Medicine and for the production and distribution of all Public Health Biological Products at Minimum Prices'. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, Acc0705.

complaints could be investigated.[24] This apparent lack of attention among at least some physicians to the proper storage of smallpox vaccine in the 1920s raises the question of how the vaccine had been stored and handled by nineteenth-century physicians and vaccinators and how this had affected its potency and effectiveness. Moreover, how did such conditions influence the medical and political debate surrounding its use?

In 1921, the first volume of *Studies from the Research Division, Connaught Antitoxin Laboratories* was published and included two original articles on smallpox vaccine that began a tradition of serious scientific research at Connaught into its ongoing improvement. The research was focused on maximizing the stability, potency and purity of the vaccine, particularly through increasingly careful attention paid to how calves were selected, tested, accommodated, washed and handled during and after they were inoculated.[25]

Despite the obvious effectiveness of smallpox vaccine, underscored by the sharp decline in smallpox incidence in Canada, the inherent production problem of bacterial contamination of Vaccinia pulp harvested from calf skin was a constant challenge that Connaught scientists focused intensely on overcoming. Glycerin was effective in sharply reducing bacterial contamination after the Vaccinia pulp was harvested and processed, but during the late 1920s, Connaught scientists focused their attention on further reducing bacterial content by improving how the calves were selected, tested, handled and kept clean before, during and after they were inoculated. More careful attention to the cleanliness of the calf stalls and their handlers made a significant difference, as did increasingly scrupulous measures of washing and rewashing the calves and the vaccinated area of their abdomen, and also the liberal use of 'brilliant green', which was a triphenylmethane dye of the malachite-green series generally used in a 1:500 dilute solution as a topical antiseptic. It was particularly effective against gram-positive microorganisms. The results of such measures in reducing bacterial content were quite clear after a 1927 series of experiments. In a vaccine with a high initial bacterial count of 30,000,000 per cc, a series of phenol-glycerine treatments reduced the count to 300, while in a vaccine with a low initial count of 3,000 per cc, phenol-glycerine treatment reduced the count to an undetectable level.[26] By 1932 an even more intensive routine of washing the calves before and after vaccination and the expanded use of brilliant green, further reduced the bacterial content of Connaught's finished vaccine, ranging from 60 to 60,000 per cc over 45 lots produced during two years of production; 17 lots had counts of less than 1,000 and 14 were between 1,000 and 3,000 per cc.[27]

By the early 1930s a new research program began at Connaught. It was led by Dr James Craigie and focused on Vaccinia and Variola strains and Vaccinia elementary bodies. Utilizing Vaccinia virus cultured in rabbits and other animals, Craigie's interests were focused on the 'flocculation reaction' evident when Vaccinia lymph, or smallpox crusts, were mixed with an appropriate antiserum. Such visible reactions with viral materials were unfamiliar to researchers at the time and had been thought to be bacterial invaders, but Craigie demonstrated that the antigen-antibody floccules in fact contained infectious viral particles, otherwise known as 'elementary bodies'.[28] By the start of World War II, other demands, including an intensive effort to produce typhus fever vaccine for the military, resulted in the slow down of Vaccinia research work at Connaught, although smallpox vaccine production increased significantly.

Interest in improving smallpox vaccines was boosted during World War II and especially through the late 1940s, by the persistent and increasing incidence of smallpox in tropical countries and by the limited effectiveness of glycerinated smallpox vaccine in such environments. Liquid smallpox vaccine was very heat sensitive and under tropical conditions it might not be properly refrigerated. A variety of freeze-dried smallpox vaccines had been produced as early as 1919, particularly in France for use in its African colonies, but it was not until after the end of the war and the establishment of the World Health Organization in 1948 that the usefulness of a freeze-dried smallpox vaccine in tropical countries grew more apparent and research efforts focused on improving production methods to boost the heat stability of dried vaccines.[29]

Dr L.H. Collier of the Lister Institute in England was one of the first to take up this challenge, adapting a centrifugal freeze-drying apparatus developed during the war for blood plasma to smallpox vaccine production. Collier's freeze-drying technique was based upon the preparation of suspensions of Vaccinia virus utilizing a method developed by Craigie in 1932. Collier used a homogeneous strain of Vaccinia first described by Dr Cleeve Russell Amies in 1938, who was then at the Lister Institute. A strain of virus was needed that could be easily purified and which would show uniform characteristics during repeated passages. Collier thus converted the standard Lister strain of vaccinia to a 'homogeneous' strain, the starting material for which was a partially purified elementary bodies suspension prepared from sheep pulp using differential centrifugation, followed by repeated passages on the skin of the rabbit.[30] Twenty years later, Amies himself was to join Connaught. Among other projects, he was to oversee the development of its first generation of freeze-dried smallpox vaccine.

Connaught had experimented with producing a dried smallpox vaccine as early as 1941, however, little more was done in this area until 1958, when a major smallpox epidemic struck what is now Bangladesh, causing more than 100,000 cases. The International Red Cross and the WHO mobilized vaccine from all over the world, including Canada, where stocks were quickly exhausted. The Canadian Red Cross approached Connaught to produce additional vaccine 'with the utmost speed'. Defries, who had retired as Director of Connaught in 1955 after overseeing its 'Herculean' Salk polio vaccine development and production program,[31] stepped in to apply his long experience with smallpox vaccine, and within four weeks Connaught had shipped 1.5 million doses.

The vaccine sent to Bangladesh was regular glycerinated vaccine, but it was clear that a dried vaccine would be more useful in such a tropical environment. After the crisis had passed, Defries stressed to Connaught's Human Antigens Committee the importance of proceeding with developing a dried smallpox vaccine.[32] At the same time, stimulated by the high profile success of the Salk polio vaccine and the beginning of work on an oral polio vaccine, considerable international attention was now focused on improving smallpox vaccines based on tissue culture methods like those being used to produce polio vaccines.

In late 1958, a research program was launched at Connaught under the direction of C.R. Amies, focused on investigating some of the new production ideas, including the development of a freeze-dried smallpox vaccine. By 1960, Amies was able to produce a dried vaccine on a small scale, and by 1962 clinical trials were conducted with the Canadian Armed Forces, as well as in the West Indies and Africa.[33] However, Amies was

more interested in research than vaccine production; he left Connaught in 1962, passing direction of the smallpox program to Dr Paul Fenje, who had worked with him since they both arrived at Connaught in 1958.[34]

Connaught Laboratories, Paul Fenje and Raising Smallpox Vaccine Standards

The growing global threat of smallpox, particularly through increasing international air travel, and the goal of eradicating this disease required fresh approaches, with energy directed at developing, producing and utilizing the best dried vaccine possible. In early 1962, Paul Fenje assumed this responsibility with a unique blend of research and production skills, enthusiasm and humility, which helped bring the global battle against smallpox to new levels of intensity.

Born in Novi Sad, Yugoslavia, in 1915, and following in the medical paths of his father and grandfather, Fenje received his MD from the University of Zagreb in 1940. He then received a Diploma in Public Health from the Institute of Hygiene in Belgrade and a Specialist in Microbiology certification. Fenje was primarily drawn to microbiology and diagnostics, and, as he later recalled, an interest in 'finding the reason or cause of why things happen' in the laboratory, rather than looking down people's throats as his father as a general practitioner did. He was particularly interested in rabies and influenza. In Yugoslavia under the Communists, Fenje oversaw a viral diagnostic lab and then a general public health laboratory in Sremska Mitrovica.

In 1955, Fenje was appointed Head of the Department for Medical Virology at the Pasteur Institute in Novi Sad, where he served until 1958, when, through some 'conspiratorial work', he and his family escaped from Yugoslavia and moved to Canada. Unsatisfied with a position that increasingly kept him behind a desk at the Pasteur Institute, Fenje accepted an invitation from the University of Edinburgh in Scotland to do some research. At the same time, his wife and children quietly managed to travel to London, where the family reunited and took the opportunity to board a steamship bound for Montreal.

Fenje needed a job quickly and first went to the Institute of Microbiology at the University of Montreal, but they had little to offer him, and neither did McGill University.

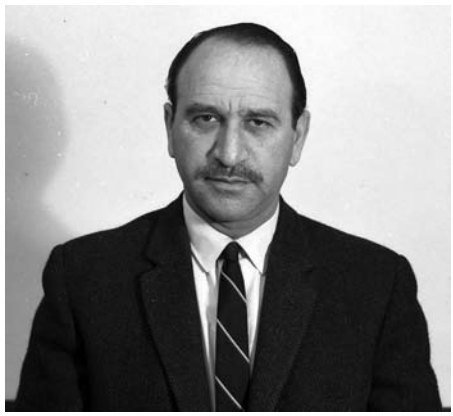

Figure 13.4 Dr. Paul Fenje, passport photo taken in 1967. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, Aneg67-35.

Fenje and his family next went to Toronto where he arranged to meet the Director of Connaught, Dr J.K.W. Ferguson. At the time, Fenje had heard the Connaught name but knew little about the Labs. Immediately impressed with Fenje's ability to speak six languages, and in need of someone experienced enough with rabies vaccine production to help stem an alarming outbreak of the disease among Eskimo dogs, Ferguson hired Fenje on the spot.[35]

Hired at about the same time as Amies and initially working under his direction, Fenje's primary focus during his first years at Connaught was on preparing and improving rabies vaccine. While he would maintain this interest in rabies throughout his career at Connaught, the development of new smallpox vaccines increasingly consumed his time. As he later recalled, Fenje was immediately overwhelmed by the kindness of his colleagues at Connaught and their readiness to help, and similarly overwhelmed by the availability of money for equipment. Formal budget plans were rarely needed and none of his requests for funds were refused, which was something quite new to him. Fenje's arrival at Connaught coincided with a period of rapid growth in the Labs fueled by large-scale production of Salk polio vaccine and the beginning of development work on the Sabin polio vaccine.[36]

In February 1962, Fenje was invited to a special meeting 'to establish priorities, space and personnel requirements for the continuation of certain projects now underway and to plan for the further development of smallpox vaccines'. There were growing export demands for glycerinated vaccine, but difficulties obtaining enough suitable calves. At this meeting, Robert J. Wilson, an Assistant Director at Connaught, felt that an expanded smallpox vaccine production program was necessary in order to place Connaught 'in the most advantageous position, should shortages develop in other parts of the world as a result of current epidemics, which seem to be gaining ground, particularly in the Congo'.[37]

Top priority, however, was to be given to further development of a dried vaccine. WHO's initial smallpox eradication program, launched in 1955, was stalled after large quantities of vaccine donated by the Soviet Union were found to be contaminated. In response, and in a context of concerns about regulatory lapses that contributed to the 'Cutter Incident' in 1955 when the Salk polio vaccine was first introduced, and then the discovery of extraneous viruses in other vaccines, such as SV40 in the Sabin and Salk polio vaccines in 1960–61, the WHO focused on developing more sophisticated international vaccine standards. Such events, among other factors, helped shape the WHO's recognition that 'biological products are usually highly complex and cannot be assayed for safety and efficacy by examining final material alone'.[38] The new regulatory process would thus involve all starting ingredients, the establishment of reference materials, and the monitoring of all stages of production. This approach contrasted with that of the Standardization Commission of the League of Nations established in 1924, the work of which was primarily focused on using biological methods to define and standardize the chemical purity of final bacterial antisera and antitoxin products (see Mazumdar this volume).

For Connaught, there was no evidence of foreign viruses in its smallpox vaccines during the production process. As noted by key members of Connaught's Human Antigens Committee, the only possible sources for viral contamination would be calves or humans. Indeed, 'such virus contamination is believed to be very unlikely since

a long history of successful vaccine production has indicated no such problem'. The Committee concluded that while a formal testing program would not be needed, there were techniques available that would enable a closer study of vaccinia virus and provide useful data for Connaught to have, including in support of statements 'that our vaccinia virus has been examined for foreign virus and found to be "clean"'.[39]

During the first years of the 1960s, the idea of smallpox eradication was accelerated in light of new epidemics in developing countries and by several alarming outbreaks in Europe sparked by cases imported from endemic areas. Closer to home, in August 1962, North American fears of imported smallpox were realized when a 14-year-old boy returning home to Toronto from Brazil via New York City developed smallpox en route, touching off an international emergency and a mass vaccination campaign on both sides of the border. Fortunately, it was a mild case and there were no secondary infections. Yet, North America's vulnerability to imported smallpox was dramatically exposed.[40]

Picking up where Amies had left Connaught's dried smallpox vaccine development, Fenje initially focused his attention on experimental processing methods. He improved freeze-drying techniques, and standardized methods of testing vaccine potency and stability, beyond the traditional rabbit scarification test.[41] Indeed, the standardization of freeze-dried vaccine was critical to Fenje. As he discussed with Wilson in late May 1962, there did not seem to be any international standard or minimal requirements established regarding the potency of vaccine that was to be freeze dried. Specifically, there needed to be potency standardization based on a specific number of plaque forming units in monkey kidney cells and pock forming units in chick embryos, as well as standardization in drying techniques, moisture content and vaccine stability. As Fenje concluded in a memo, 'These are Dr. Wilson, the most important questions, which if you could discuss with the WHO experts, the resulting information might be of considerable help for the development of our dried smallpox vaccine'.[42]

The pace of Fenje's work accelerated during the latter half of 1962, boosted by the Toronto smallpox scare and by intensified international efforts to develop a dried vaccine that would meet the new WHO standards. As a self-supporting part of the University of Toronto, and in the wake of its pioneering polio vaccine work over the previous decade, Connaught was in a fortunate position to share its progress in the spirit of academic and practical inquiry, and also benefit from the advances made by others. Sharing of experience was from Connaught's perpective, largely unidirectional as they provided critical research capacity to vaccine manufacturers, including the Lister Institute in England, who were interested in obtaining samples of the Vaccinia strains Connaught was using, and the Serum Institute in Copenhagen, who were impressed with the vaccine yields Connaught was obtaining.[43] In addition, Connaught was occasionally asked to test smallpox vaccine batches sent from US manufacturers, particularly to confirm potency or stability test results.

Fenje's relationship with his international colleagues, and his position among them was elevated significantly through an International Smallpox Vaccine Symposium hosted by the Institut Mérieux in Lyon, France, in December 1962. However, Fenje had not yet been granted Canadian citizenship and was nervous about traveling back to Europe for fear of attracting attention in Yugoslavia. He also did not yet feel particularly confident in his position as a smallpox vaccine expert, confiding to Wilson shortly after being invited to the conference, 'It seems the best people in the field of smallpox control

will be present (with my exception). The problems to be discussed are all of practical importance and conclusions will have probably a significant bearing on the future development of the smallpox vaccine'.[44] Nevertheless, Fenje's paper, entitled 'Stability of Dried Smallpox Vaccine at Various Temperatures', was well received, although, as he reported to Wilson, it was scheduled during the last session of the meeting and there was very little time left for discussion.[45]

Following the conference, Fenje spent the next few weeks visiting a variety of European vaccine manufacturers and laboratories, including the Pasteur Institute in Paris, the Lister Institute in England, and the National Institute of Public Health in Bilthoven in the Netherlands. He was particularly impressed by the use of Arcton, a fluorocarbon,[46] at the Lister Institute for purifying calf pulp without high-speed centrifugation, although Fenje recognized that this process did not result in a sterile dried vaccine product. Of more immediate interest was the new Vaccinia unit at Biltoven, which produced low bacterial count pulps and used antibiotic sprays. As Fenje later wrote to the Institute's Director, Dr B. Hoffman, 'We realize now how primitive our way of handling the animals is in comparison with your methods, and we would like to do something about it, to improve it to some extent'. Fenje also asked for Hoffman to send descriptions of the Institute's filling machinery and a simple plan of its animal quarters, although Fenje recognized that, at present, he did not anticipate Connaught would have the means to build new animal quarters.[47]

Fenje's dried smallpox vaccine development work continued through 1963, albeit on a relatively small scale during the first part of the year as the uncertainties of the export market made it difficult for Connaught to commit the necessary resources for large-scale production. The WHO had not yet committed to an expanded eradication program, although, encouraged by a series of clinical trials, the Canadian Armed Forces considered converting to dried vaccine if Connaught could supply it within the next 1–2 years. Nevertheless, as was stressed at a February 1963 meeting of the Human Antigens Committee, 'C.M.R.L. should remain in the forefront of the work leading to the best available smallpox vaccine on a production scale'.[48]

In April 1963, Fenje's leadership of Connaught's smallpox vaccine development and production work was solidified with his invitation to join the Human Antigens Committee.[49] Key priorities for Fenje were preparing an application for a Canadian license for dried smallpox vaccine and also a US license. There was also interest from a US firm known as Panray, to distribute Connaught's smallpox vaccine to take advantage of American efforts to increase smallpox immunization levels.[50]

During his first full year Fenje focused almost totally on dried smallpox vaccines development and production, and was then able to recommend that routine production could begin. By June 1963, as he wrote in his first annual research report, considerable international progress had been made recently in dried vaccine production. However it was clear that there were wide variations in vaccine quality, particularly in the levels of bacterial contamination, and in how much, or how little, producers did about it.

In particular, Fenje noted that vaccine producers in Holland, France, South America, among others, seemed to be doing little to minimize bacterial contamination. They simply homogenized and then freeze-dried calf pulp without any further preparation other than adding a stabilizing agent. The resulting final product contained a relatively high concentration of a bacterial agent that caused a significant loss in potency during freeze-drying and decreased

stability when exposed to higher temperatures. Fenje also noted that 'a huge amount' of dried smallpox vaccine from the USSR donated to the WHO had to be discarded 'since it was so heavily contaminated'. However, 'some producers have sterile products of satisfactory potency, stability, purity and distributed with elaborate means for application', such as the US Army, while others, such as the Lister Institute, 'do not pay any attention to this'.[51]

The rest of Fenje's report detailed the efforts employed at Connaught to control contaminants in the final vaccine, including keeping inoculated calves under the most meticulous sanitary conditions through scrupulous washing, cleansing and scrubbing prior to exsanguination. Contamination control was also reinforced by spraying the inoculated site of each calf with a 1/1000 dilution of brilliant green, while antibiotics, 0.02% Streptomycin and 0.01% Neomycin, were used in the processing and purification of the harvested and homogenized Vaccinia pulp. The pulp was then subjected to a series of differential high-speed centrifugations, after which 10% peptone and 4% phenol solutions were added. Fenje also stressed the adoption of a standard potency of 10^8 pock forming units per ml, that would ensure 100% 'takes' in vacinees and also leave a safety margin to cover potency loss during storage at high temperatures.[52] He noted that it had been 'generally observed that vaccines containing between 5 x 10^7–10^8 infectious units per milliliter will give 100% takes, and those containing approximately 2 x 10^8 infectious units will vaccinate successfully on 50% of susceptible persons'. Nevertheless, it was clear that a positive take will render to the vaccinee a degree of protection which is independent of the potency of the vaccine'.[53] Meeting such a standard, and more importantly, meeting it consistently from lot to lot was a significant challenge for smallpox vaccine manufacturers, including Connaught. As his experience grew, however, Fenje was able to maintain and exceed such a standard over time.

Confident in his methods to produce a superior dried vaccine, Fenje faced growing pressure to expand production, particularly as the WHO worked towards intensifying its smallpox eradication program. In January 1964, Fenje was asked whether or not Connaught was prepared to supply 5 million doses of dried vaccine, should the WHO ask for it. The limiting factors he faced were the present production facilities, and an available support staff of only two or three. Calves could be processed weekly and about 44 calves would be needed to prepare the 15,380 grams of pulp required to make 5 million doses of vaccine.[54]

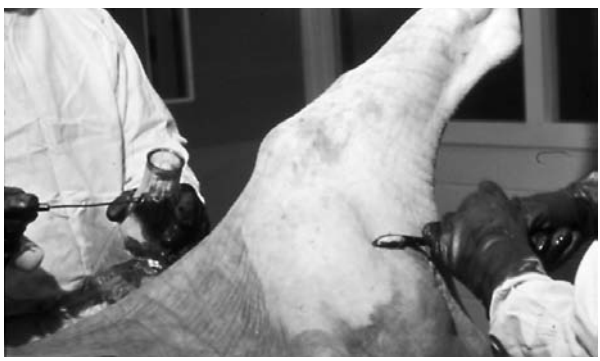

Figure 13.5 Harvesting Vaccinia pulp from calf, Smallpox Vaccine production, 1970s, Connaught Medical Research Laboratories. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, uncatalogued slide.

Fenje's confidence underscored the growing breadth of his intellectual and practical grasp of the broader situation regarding the production of smallpox vaccines around the world. During the early 1960s, he spent considerable time investigating the relative merits of the other, more 'modern', types of smallpox vaccines – that is, various tissue culture-based vaccines, and others based on inactivating the Vaccinia virus using various chemical agents or physical methods – that were being developed and promoted widely. He summarized his critical views on the state of the art in a 1964 paper, 'Advances in the Immunoprophylaxis of Smallpox'.[55] Fenje saw the theoretical advantages of some of these new approaches, however, they seemed limited when it came to adapting them to the practicalities of large scale production and quality control demands, and fell short of the immunological response shown with the 'traditional' calf-skin Vaccinia pulp-based vaccine. Fenje's progress was also acknowledged in August 1964 with the Canadian licensing of Connaught's dried smallpox vaccine, and in December by the news that it also met WHO's new dried vaccine standards.[56]

By the summer of 1965, the intensity of smallpox vaccine production at Connaught increased after the announcement that the United States government was prepared to sponsor a more sophisticated global smallpox eradication program through the WHO.[57] There were also new inquiries about how much dried vaccine Connaught could supply and how soon. A new smallpox building was under construction to enable larger production, but it would not be ready until late in 1965.[58]

At the same time, the WHO Assembly issued new measures concerning the international control of smallpox, yellow fever and malaria, requiring that all vaccinations for international certification should be made only with a product certified to fulfill WHO vaccine requirements. This meant that, as of 1 January 1967, anyone traveling between countries that required proof of smallpox vaccination or re-vaccination had to present an official vaccination certificate that included information about the origin and batch number of the vaccine they received.[59]

Fenje felt that there were no major differences between the current Canadian and WHO dried vaccine standards, although the WHO was now calling for a more potent vaccine than Canadian regulators required. In September 1965, Fenje stressed to Wilson that Connaught needed to upgrade its present criteria for acceptance in order to meet all of WHO's requirements, which meant increasing the concentration of the vaccine, although this would increase its production cost. At the same time, Connaught had to meet US requirements, which differed substantially from Canadian and WHO regulations with respect to potency testing procedures; American authorities only required the rabbit scarification test, which involved comparing the scratched skin reactions of a series of vaccine samples of varied dilutions. This was also the only test that provided a good indication of the vaccine's effect when applied to human skin. This test required three times as many animals as Connaught's.[60]

In order for Canadian travelers to prove their smallpox vaccination status when they crossed international borders, Canadian regulatory authorities had to certify that Connaught's vaccine met the new WHO standards, and there were concerns that it might not in light of the WHO's reliance on the pock count test, which indicated a vaccine that was perhaps not potent enough, while other tests, and reports from some doctors suggested that it was too potent. It was evident to Fenje, however, that the potency of the vaccine was not related to its potential reactivity; increased reports of

reactions were more related to increased reporting sensitivity than to a more reactive vaccine. The new testing and certification rules proved frustrating to Fenje. As he stressed in a handwritten note to Wilson in response to a letter from R.A. Chapman, Director General of the Canadian Food and Drug Directorate, 'I think it would be entirely impractical from anybody's point of view to deal with 2 kinds of vaccines: 1) one which would be certified and to be used for the International Vaccination Certificate, and 2), another vaccine, non-certified for "non-international" purposes. It seems to me, what we have to do is to prepare the smallpox vaccine so as to meet in every lot their requirements'.[61]

By March 1966, Connaught's smallpox vaccines met all US and WHO requirements, each batch subjected to rabbit scarification and the pock mark tests.[62] Meanwhile, the preparation of a dried vaccine suitable for use with the jet injector would have to meet another set of strict WHO standards, particularly for sterility and consistency in light of the different dosage and delivery system involved. As Dr Donald A. Henderson, Director of the WHO Smallpox Eradication Program, pointed out to Wilson, 'I argued some tolerance in the requirements but it was quite clear the Committee was against bacteria like sin and to advocate some low level of bacterial contamination was akin to arguing the virtues of wine to a group of Methodist clergymen. It's a funny world'.[63] The jet injector for smallpox vaccine was introduced in the early 1960s, initially for use in the US and Canadian military, and involved a special intradermal nozzle designed for use with a hypodermic jet injector apparatus that provided a very rapid method of intradermal injection. When used instead of the traditional multiple pressure method, the vaccine could be diluted 50-fold, thus greatly boosting the efficiency of mass smallpox vaccinations.[64]

Fenje's primary goal was, however, to produce a dried smallpox vaccine that was truly bacteriologically sterile, that is with consistent bacterial counts of 0 in each vaccine lot. By early 1968 Fenje was able to confidently make such a claim. Yet, as early as October 1965, the President of Wyeth Laboratories had personally phoned Connaught's Director, J.K.W. Ferguson, inquiring about the sterility of Connaught's freeze-dried smallpox vaccine. As Wilson reported to Fenje, Wyeth's President had heard a rumour that 'we were producing sterile material for the jet injector', while Wyeth had one contaminated dose for every 200 it produced.[65] 'I don't think we ever claimed that our dried vaccine is sterile', Fenje replied to Wilson, 'although in practice we always tried to achieve this goal. It just happened that the standard tests used for both the glycerinated and for the dried smallpox vaccine did not show any bacterial contamination'. He admitted at the time, however, 'it is quite possible that the vaccine would not pass a rigorous sterility test'.[66] In February 1968, Fenje reported to Connaught's Human Antigen Committee that 9 sterile lots of dried smallpox vaccine had been produced, representing about 1 million doses. In addition, several countries, including Chile, were interested in buying 1.5 million doses of the sterile product.[67] US regulators were also impressed with Connaught's dried smallpox vaccine. In a series of sterility tests in October 1970 at the National Institutes of Health in Washington, they were able to pass at least 1,100 doses of Connaught's dried vaccine through a 0.45 micron pore-size Millipore filter without clogging the filter and with no evidence of contaminants.[68]

The WHO permitted a bacterial count of up to 100 non-pathogenic contaminants per cc of smallpox vaccine. By the late 1960s, Fenje was consistently able to demonstrate

bacterial counts of 0 in virtually every Vaccinia pulp he processed. From January 1970 through February 1976 – which included the period of peak production of some 35 million doses of dried smallpox vaccine primarily for the WHO – only 8 out of 179 fully processed Vaccinia pulps prepared for all vaccine types had bacterial counts that were not 0, and they only occurred sporadically among the first 26 pulps processed between January 1970 and February 1972. The highest bacterial count recorded was 29 per cc (which was the first pulp of the series, but well under the WHO standard of 100 per cc) and the others ranged from 2 to 18; all counts were 0 for each of the remaining 150 Vaccinia pulps processed after February 1972. This smallpox vaccine purification process generally began with initial homogenized Vaccinia pulps with bacterial counts ranging from as low as 6 for pulp #872 (processed in November 1970), up to as high as 50,600,000 for pulp #977 (processed in May 1972), although the average initial count ranged from a low of 1,000 to 100,000 over the 6 years of vaccine production that are well documented.[69]

Fenje's sterile freeze-dried smallpox vaccine took 3 days to prepare, followed by a variety of tests. On the first day one part crude calf pulp was suspended in three parts 0.004 M McIlvaine buffer (with no antibiotics), and then homogenized and centrifuged, resulting in Extraction #1. The supernatant was kept and the sediment used for preparing Extractions 2, 3 and 4, which followed the same process as #1 with the exception that antibiotics were added to the McIlvaine buffer (10 mg% of Neomycin and 20 mg% of Streptomycin). After Extraction #4 the remaining sediment was discarded. The four extractions were then pooled and subjected to three cycles of purification by differential centrifugation, after which the sediment was discarded and the purified pooled extractions stored overnight and then subjected to high-speed centrifugation. The supernatants that contained the antibiotics were then discarded and the final elementary body suspension of Vaccinia virus was prepared from the remaining pellets, which were then re-suspended in the McIlvaine buffer, but without the addition of antibiotics, and then pooled and homogenized. Peptone and phenol solutions were then added and the suspension left at room temperature for 24 hours under constant stirring. The Vaccinia suspension was generally sterile at this point. A peptone solution was then added to decrease the phenol concentration (which lessened the harmful effect of phenol on the Vaccinia virus) and the final suspension stored at 0° C until all bacteriological and potency tests were completed and passed and the filling and freeze-drying process could commence.[70]

Connaught's smallpox production process was not a secret. As noted earlier, there was considerable sharing of information with other smallpox vaccine producers, including Wyeth Laboratories, which was the largest producer of smallpox vaccines in the US. After Fenje sent a copy of Connaught's standard procedure for dried smallpox vaccine, Wyeth prepared a summary document comparing Connaught's and Wyeth's production and testing process. Wyeth's Managing Director, J.H. Brown, felt that 'Apparently there are no great differences between our two laboratories'. Nevertheless, there were interesting differences in the handling of the calf before inoculation: Connaught sprayed the inoculation site with acetone and also injected 40% chloral hydrate as a general anaesthetic, while Wyeth did not use acetone, but rather rinsed the calf with 70% alchohol and did not use any anaesthetic unless the animal was uncontrollable. Connaught used wooden platforms to hold the calves for inoculation to minimize soiled

vaccinated areas, as well as sterile sawdust spread on the floor. At Wyeth, in contrast, sawdust was not used, while the calf was 'held on metal slatted rack but probably too close to floor for maximum effectiveness'. As noted earlier, brilliant green (containing added neomycin and streptomycin) was employed quite liberally at Connaught before and after Vaccinia inoculation, while at Wyeth, brilliant green was not used since 'attempts at using it did not substantially reduce plate counts of the skin swabs or harvested pulp'; also, antibiotic sprays were not used at Wyeth.

During the preparation of the purified Vaccinia suspension, other important differences are evident. At Connaught a total of 4 extractions were made, the homogenate centrifuged at 1200 G for 10 minutes; at Wyeth 3 extractions were made with centrifugation at 1000 G for 15 minutes, with both labs employing neomycin and streptomycin in the buffer. In contrast to the further purification processing at Connaught described earlier, at Wyeth, there was no further purification conducted after the initial low speed centrifugation, but rather treatment with 0.5% phenol and holding for 5 days at 4° C, followed by centrifugation at 5000 G for 2 hours. There were also several differences in the tests that were conducted on the final vaccine. For example, Connaught tested for *Bacillus anthracis*, while at Wyeth no test was done as they felt this would be 'picked up on blood agar'. Also, intratesticular injections of rabbits were done at Connaught with observation for local reaction or generalized infection; at Wyeth no such test was conducted.[71] Wyeth's Managing Director may have felt that these differences were insignificant, but they do highlight important differences between the two labs: in the level of care taken with the handling of the calves, in the level of rigor employed in the processing and purification of Vaccinia pulps, and in the testing of the final vaccine. Connaught had a stronger academic orientation and focused more attention on vaccine development and production. Wyeth, in contrast, had a purely commercial structure; pharmaceuticals were the major product line, and vaccines played only a small part. This different emphasis may explain at least some of the differences.

Connaught and the Politics of Smallpox Eradication, 1967–1979

Despite the WHO's desperate need for such a high quality vaccine as the global smallpox eradication program began, the Canadian government was unable, or unwilling, to buy the vaccine from Connaught and donate it directly to the WHO. Canadian politics and External Affairs regulations that only permitted general financial support to the WHO was a source of growing frustration for Henderson, Wilson and Fenje. Henderson had earlier suggested to Wilson, 'A donation to the Organization of perhaps 5 to 10 million doses of vaccine for jet injection (100 dose vials) would really be a Godsend. The [limited] availability of vaccine for jet injection is going to put us in a real bind before long. Any hope?'[72] Eight months later, Henderson again stressed to Wilson, 'With your tremendous capacity and good vaccine, I am sorry not to see it more extensively used'.[73]

The most intensive year of Connaught's involvement with the eradication effort was the first, 1967–68, during which Wilson and Fenje, as special consultants to the Pan American Health Organization, visited some 15 labs in 12 countries of Latin America to help improve local vaccine production quality. At Connaught, which was designated

one of two International Smallpox Vaccine Reference Laboratories by the WHO, Fenje also hosted a series of scientists and technicians from Latin American vaccine producers to further instruct them on vaccine production methods. Indeed, it was clear that the quality and purity of locally produced vaccine in Latin American countries, as well as most of the 30 other smallpox endemic countries, was much poorer than expected.[74]

The newly established WHO vaccine production methods and standards, based largely on the initiative of Wilson and Fenje and the experience of Connaught, were codified in 1968 in the WHO's *Methodology of Freeze-dried Smallpox Vaccine Production*.[75] In September 1968, after another trip to South America, Wilson reported to Henderson, 'The WHO "Methodology" was received with great enthusiasm and everyone agreed that it was a most useful document even though they do not all follow the precise procedures'. He was 'most gratified to see such progress in about one year, (since my last visit) and the enthusiasm [with which]these people have attacked the problem in spite of economic, political and administrative chaos'.[76]

Meanwhile, a certain level of political and administrative chaos in Canada continued to complicate the WHO's use of Connaught's vaccine. However, some unexpected and somewhat embarrassing press attention in May 1970, featuring 'an eloquent presentation' by Henderson on television of the need for smallpox eradication and for the need for vaccine,[77] finally prompted the Canadian government to donate 7 million doses of Connaught's vaccine to the WHO.[78] According to Henderson and Wilson,

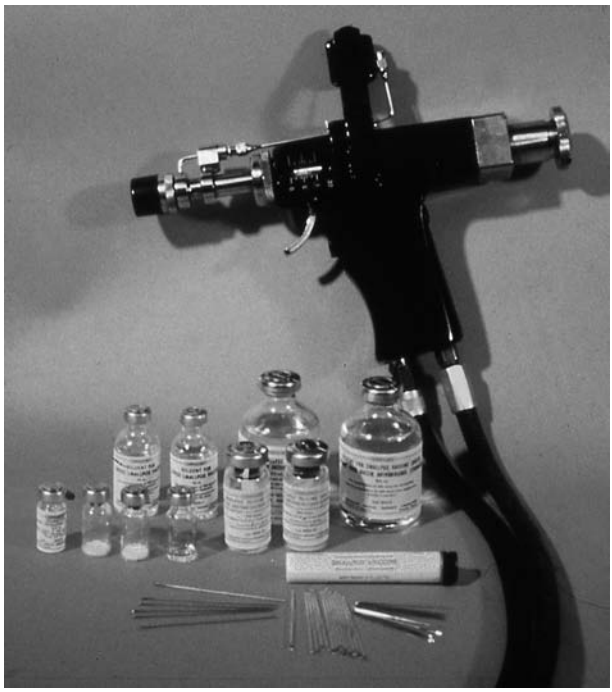

Figure 13.6 Jet injector and smallpox vaccine (dried) vials and needles, Connaught Medical Research Laboratories, 1970s. Source: Sanofi Pasteur Limited (Connaught Campus) Archives, uncatalogued slide.

this TV story had a 'long and colourful' background. Earlier, the Canadian Mission to the United Nations had approached Henderson in support of bilateral donations based on specific requests for aid. Henderson, however, stressed the far greater flexibility of a multilateral donation, directing vaccine to where it was needed most.[79] As Henderson recalled, 'The man at the Mission seemed a bit troubled by this (for reasons I do not know) but when informed that the approximate cost of the vaccine would be in the range of one cent per dose and that we were talking of only 85,000 dollars, he rather snorted at the various proposed restrictions, etc. suggested by CIDA'.[80]

At about the same time, Wilson had a dinner guest of his niece's at his home. Wilson later discovered that he was a television producer. 'At her prompting, I told him about some of the problems related to the smallpox process, amongst these was the stupidity of the Canadian government over a donation of smallpox vaccine'.[81] In June 1970, shortly after this media attention to the issue, the Canadian International Development Agency asked Connaught to provide a quote for 8.5 million doses of smallpox vaccine for the jet injector. Wilson was 'hopeful that the machinery is now grinding'.[82] By August 1970 there were still a few more details to iron out, but it was clear that the Canadian government was now committed to donating $140,000 to purchase about 7,000,000 doses of dried smallpox vaccine from Connaught.[83] The priority for the first vaccine shipment was Ethiopia and the Congo.

Henderson's main concern in October 1970 was to obtain as much vaccine for the Canadian donation as possible, for use in the jet injector, as well as with the bifurcated needle. As he stressed to Wilson, 'Believe it or not, we are desperately in need of vaccine in quantity for this programme', but hoped Connaught might be able to offer a better price. In particular, Henderson pointed out that 'the costs for [Connaught's] jet injection vaccine, for example, are considerably higher than comparable vaccine from any other source, even Wyeth!' Wilson agreed, but pointed out that 'our process is more costly than other preparations and this is reflected in the very high quality of the vaccine as claimed by NIH. I think we cannot make any short cuts in this processing'.[84]

The bifurcated needle for multiple puncture smallpox vaccination was originally developed at Wyeth Laboratories by B.A. Rubin in 1961. While the jet injector 'marked the peak of complex vaccination technology', historian Derek Baxby has suggested that 'the bifurcated needle marked the peak of simple excellence'.[85] The bifurcated needle was based on a sewing needle with the ends of its loop cut off and then ground to a point, the idea being, as Rubin recalled'that a pronged needle would retain the capillary activity of a loop and that it might have simultaneous utility in scarification'. Simplicity and economy were the bifurcated needle's main advantages as it could be used by almost anyone after minimal training – although in the hands of an expert made possible 800–900 vaccinations per day per vaccinator – plus the 'capillary action held enough vaccine for one dose between the prongs, a saving of 75% in the volume used for other techniques'. After use the needle could be quickly sterilized, or was cheap enough to be easily discarded. Connaught, however, was unable to utilize the bifurcated needle in its dried smallpox vaccine package due to Wyeth's patent protection. In 1968, in support of the smallpox eradication program, Wyeth waived its patent royalties from the bifurcated needle, shipped them in bulk to Geneva, and allowed the WHO to utilize it freely with all dried vaccines used where smallpox persisted, including Connaught's.[86]

Nevertheless, Henderson remained desperate for vaccine. Indeed, as he stressed to Wilson, 'we are in need of vaccine in fairly large supply and on a continuing basis particularly for the programme in the Congo. Vaccinating as if it was going out of style, consuming vaccine at a prodigious rate – faster by far than we had anticipated earlier'. Henderson preferred to use Connaught's vaccine, 'as it makes it most difficult for the field units to change from one type of vaccine to another – more specifically from the very practical Canadian package to others which are far more cumbersome'.[87]

By February 1971, Henderson's vaccine supply concerns eased when Fenje was pleased to report, 'I have just completed the production of your order. I guess that you will shortly have on hand about 10 million doses of the best dried smallpox vaccine ever made in our Galaxy'.[88] Henderson was 'indeed delighted' and claimed that 'with a continuing flow of this vaccine, I would hope that we would be battling the problem of smallpox in Sudan and Ethiopia (in Africa) by the end of this year'.[89] A few months later, Wilson wrote to Henderson, 'Paul Fenje has recently been asking me whether there have been any reports from the field on his "best vaccine in the galaxy". I think he is rather anxious to know how it is performing although I have few doubts this properly applied will do what is expected of it'.[90] Henderson was very pleased. As he told Fenje, 'Your vaccine, incidentally, is performing magnificently both in the Congo and Ethiopia. The good packaging and ease of reconstitution have both been commented upon. Take rates in primaries have been in the range of 98% to 100%'.[91]

As he stressed in a recent interview, Fenje was quite serious in his claim of galactic supremacy of his dried smallpox vaccine. His ability to consistently prepare a sterile dried vaccine impressed the Canadian and American regulatory authorities as well as the WHO. They were also all similarly impressed with the unique Freon-purified liquid glycerinated vaccine he was also able to regularly produce for Canadian use.[92] Developed in 1969 by Fenje, Connaught's Freon-Purified smallpox vaccine was prepared in the same manner as the standard glycerinated product, but was purified by treatment with Freon (113) to remove proteinaceous cellular debris. The product was thus 'purified' and finished as a 'sterile' vaccine. No antibiotics were used in the preparation, and with the addition of tests for sterility, protein content and residual Freon, the remainder of the testing process was the same as for Connaught's regular glycerinated product. The Freon-purified vaccine was also considerably more stable and hence had a longer expiration dating than the standard product.[93]

By 1971 remarkable progress had been made in the global smallpox eradication program, particularly in Latin America. Smallpox was clearly on the run. However, a 'high emergency' situation in Bangladesh in 1972 reminded everyone about the persistent threat of smallpox. Connaught responded with a commitment of 5 million doses of vaccine. As Fenje said to Wilson, 'D.A. [Henderson] is urging us to cut down the time for our testing to the minimum and to shorten as much as possible the administrative process regarding vaccine delivery'.[94] At about the same time as the Bangladesh epidemic, smallpox was imported into Yugoslavia, sparking a serious outbreak of 170 cases and 40 deaths, further reinforcing the importance, particularly for the Yugoslavian-born Fenje, of establishing national smallpox vaccine stockpiles.[95] After considerable debate over the type of vaccine to be used – glycerinated or dried/jet injection or multiple pressure – how much vaccine to prepare and at what price, by 1974 Connaught had prepared a 1 million dose dried smallpox vaccine stockpile for the Canadian government.[96] By early

1979, however, it was clear to Fenje that a new stockpile would be soon needed.[97] At the same time, the WHO proposed that a 25-million-dose stockpile be prepared and held at Connaught for emergency use in Latin America.[98] Thus, in March 1979, and aware of his forthcoming retirement, Fenje quickly pressed ahead with the preparation of 17 Vaccinia pulps for these new stockpiles.[99]

As is well known, the last stand for smallpox took place in Somalia, the final natural case occurring on 26 October 1977. After two years of careful surveillance for additional cases of smallpox in Somalia or elsewhere, none were found. Smallpox, 'the speckled monster', was vanquished. On 26 October 1979, Africa was officially declared free of smallpox, with global eradication formally declared by the WHO on 9 December 1979.[100]

The timing of the official declaration of global smallpox eradication coincided with Fenje's retirement, prompting reflection by his colleagues on his contributions to this unprecedented effort in medical history. As D.A. Henderson's successor at the WHO, Dr Isao Arita, said of Fenje in a letter to Wilson,

> As you will remember, at the beginning of the programme in 1967, the quality of many vaccines was not good. In three years, the quality had been rapidly improved and since then the eradication programme has employed potent and stable vaccine. You have been the principal scientist in the WHO Collaborating Centre for this excellent development. Your contribution was considerable. The supply of quality vaccine has, in fact, been one of the major elements which led to the successful eradication of the disease.[101]

Henderson also recalled, 'I appreciate only too well how many of the concepts in the execution of the smallpox program saw the first light of day over a glass of beer with Bob [Wilson] and Paul [Fenje]. What I don't recall is whether the ideas stemmed from Wilson or Fenje, so perhaps they are better attributed to Wilje (or should it be Fenson?)'.[102] Moreover, he felt that 'Directly and indirectly, the ammunition for the campaign bore the indelible stamp – "made in Canada". To a once-Canadian, it was always a personal source of pride'.[103]

With smallpox officially eradicated, Connaught began the process of shutting down its smallpox vaccine production facility, the last lots completed in March 1980 for the new Canadian stockpile.[104] However, the large stockpile the WHO had proposed was abandoned due to lack of Canadian government sponsorship. Thus, in April 1980, 15 Vaccinia pulps remained in deep freeze storage, along with other materials such as seed virus and samples.[105] The shutdown of Connaught's smallpox department was scheduled for July 1980 and included plans for the incineration of the remaining pulps and materials; it was expected that any future smallpox vaccine would be made by using cell culture adapted seed virus.[106]

In September 1980, however, Connaught's Medical Director, E.W. Pearson, strongly recommended that Vaccinia pulps should be kept. As he stressed, 'It surely will not be a great problem to keep the seed virus and pulps for some time to come and at least in this way we might have something to fall back on so as to be able to prepare our licensed product'.[107] These Vaccinia pulps were indeed saved and kept in the deep freeze, undisturbed, for the next 21 years. The terrorist attacks of 9/11 prompted their retrieval, testing and careful processing to expedite the preparation of a new Canadian smallpox vaccine stockpile.

At the first Canadian Conference on Counter Terrorism and Public Health, held in Toronto in late October 2003, a special honour was given to Drs Paul Fenje, R.J. Wilson and D.A. Henderson by the Canadian Public Health Association and Aventis Pasteur Limited (now Sanofi Pasteur Limited). R.J. Wilson had retired from Connaught a year after Fenje, but died suddenly in 1989. His son, Ray Wilson, who also worked at Connaught for many years, accepted the honour on behalf of his father. This honour and rare reunion of the Fenje, Wilson and Henderson team, like the new Canadian smallpox vaccine stockpile, would not have occurred if not for the foresight of Pearson to keep the pulps Fenje had made in 1979, and for the confidence Aventis Pasteur had in their quality that was evident from the extensive archival record Fenje had left of his work. Indeed, my role as a professional historian and my familiarity with this archival record was also significant in a practical way, first in establishing the extensive historical context surrounding the preserved Vaccinia pulps that enabled the new smallpox vaccine stockpile to be prepared with confidence, and, secondly, in providing the wealth of primary documentation from which I was able to assemble this story.

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3 A core, though unorganized, archival document, clippings and image collection was retained in the Connaught Library through the 1970s and early 1980s, assembled rather randomly from the donated or found files of former Directors and leading researchers and staff. By 1983 this primary collection had been more formally organized under the leadership of Dr Robert J. Wilson after he retired from a long career, which included serving as Director and Scientific Director of Connaught from 1972 to 1980. Wilson was also a central figure in Connaught's smallpox vaccine story. Historians have been able to access this collection since the early 1980s with minimal restrictions. Also retained, though not as easily accessed, or as well catalogued, is a vast collection of records stored off-site; the main collection, once kept in the Connaught Library is now stored off-site. I first became familiar with this material in the early 1990s while researching my dissertation on the history of polio in Canada. As a historical consultant for Connaught since 1995, I have utilized these archival collections through many heritage projects at the company and for others, as well as for a variety of more academic, research-oriented projects of my own. The present paper is based primarily on the large off-site archival collection and grew out of both types of projects. See Christopher J. Rutty, 'Do Something! Do Anything! Poliomyelitis in Canada, 1927–1962', Ph.D. Thesis, University of Toronto, 1995. For some personal perspective on how I became familiar with Connaught's archival collection, see Christopher J. Rutty, 'The Canadian Polio Experience: A Personal Journey Through the Past', *Ars Medica*, **1**, 2005, pp. 60–73.

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