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10. The spread of bacterial infection, the problem of herd immunity

Topley WWC, Wilson GS. J Hyg 1923; **21**: 243–249

AN APPRECIATION BY PAUL FINE

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This paper [1] is a milestone in the literature on infectious diseases. To put it in context, we recall that the late 19th century saw the construction of the germ theory, and its ultimate acceptance by the medical profession. The massive research effort led by Pasteur and Koch and their followers demonstrated a variety of infectious agents, catalogued their properties, and traced their pathogenesis in infected hosts. An understanding of the behaviour of infections in populations came only later, in the early 20th century, exemplified in the work of Ross on malaria [2], which was extrapolated to all infections in his 'theory of happenings' [3], and of Hamer on measles [4]. But there remained a tension between those who viewed infections from the perspective of the laboratory, with its emphasis upon biological properties, and those who viewed disease from the perspective of population statistics [5], which lent itself to more abstract and mathematical descriptions of epidemiological patterns. Fierce battles were waged between these disciplines, as between Almroth Wright and Karl Pearson on the subject of typhoid vaccination [6, 7].

Among the outcomes of this tension were large research efforts which aimed to explain population patterns of infectious diseases in terms of measurable properties of the infectious agents. This work was carried out mainly between 1915 and 1930. It involved the study of infections in laboratory populations of mice, and described itself as 'experimental epidemiology'. In the United States the effort was led by L. T. Webster, carried out within the Rockefeller Institute in New York, and published in a major series of papers in the *Journal of Experimental Medicine*. In the United Kingdom the research was carried out as a major programme of the Medical Research Council, led by W. C. C. Topley and G. S. Wilson, and published in an important series of articles in the *Journal of Hygiene*. Topley and Wilson were among the most distinguished bacteriologists in the world – their *Principles of bacteriology and immunity* [8], first published in 1929 and now in its ninth edition (as *Microbiology and microbial infections* [9]), became the standard text in the English language, and Wilson was to become the first Director of the Public Health Laboratory Service on its founding in 1941.

Their approach involved setting up populations of mice, controlling their demography (adding animals according to a defined timetable), introducing one or another infectious agent (in particular *Bacillus* – now *Salmonella – enteritidis* or ectromelia virus), and monitoring the result. A vast amount of effort went into detailed parallel bacteriological studies, and literally tens of thousands of mice were autopsied in these experiments over a period of almost two decades. Among the questions posed in the course of this research was whether periodic epidemics within the animal populations were associated with parallel changes in the infectious agents. Such changes were not found, and the work as a whole was important in confirming the importance of demography – populations' size, and the rate of influx of susceptibles, as important determinants of infectious disease patterns in populations [10].

The paper selected for this compilation is one from this series. It reports two particular sets of experiments which involved comparisons between populations made up of different proportions of susceptible and 'immunized' mice. In simplest terms, the results showed that the higher the proportion of immunized animals at the start, the slower was the course of the epidemic and the lower was the mortality. Today's reader will not be surprised by these findings,

although we may wonder about the nature of the immunity induced in the vaccinated mice. If numerically inclined, today's reader will be disappointed by the analysis and discussion (for example the failure to separate immunized from non-immunized mice in the mortality table). But that would be to miss the point.

This paper was the first to articulate a fundamental problem in infectious disease research and control, and introduced a term which is still widely in use today – 'herd immunity'. The authors describe their evolving thoughts early in the paper:

> Consideration of the results obtained during the past five years, both in experiments which have formed the subject of reports and in many others not yet recorded, has led us to believe that the question of immunity as an attribute of the herd should be studied as a separate problem, closely related to, but in many ways distinct from, the problem of the immunity of an individual host.

And they closed by posing an even broader and very practical challenge:

> One obvious problem to be solved is the following. Assuming a given total quantity of resistance against a specific bacterial parasite to be available among a considerable population, in what way should that resistance be distributed among the individuals at risk, so as best to ensure against the epidemic spread of the disease, of which the parasite is the causal agent?

This is a superb question. Its full appreciation by the research and public health communities would take several decades, becoming a major theme only in the 1970s, stimulated by the increased use of vaccines and in particular by the global effort to eradicate smallpox. A theoretical solution was hinted at by Gordon Smith [11], and articulated elegantly by Klaus Dietz [12], who showed that the critical proportion to be immunized (for the elimination of an infection, assuming permanent solid immunity and random mixing) could be estimated as one minus the reciprocal of the basic reproduction number, a theory which was then expanded in the work of Anderson and May [13] and many others [14]. In the real world, public health officers involved in disease control found solutions in terms of transmission patterns and field logistics – the use of active surveillance and ring vaccination proved the key to smallpox eradication [15], and national immunization day campaigns are the mainstay of the current global effort against polio [16]. All of these are separate, good, important answers to the question posed by Topley and Wilson in this paper [1].

Some years ago I had an opportunity to talk with (Professor Sir Graham) Wilson about this work, and I asked how he and Topley had come upon the phrase 'herd immunity'. He reflected, and told me that it had arisen in the course of a conversation with Major Greenwood 'over tea'. Interestingly, it was Greenwood who would first-author the 1936 MRC report summarizing the two decades of experimental epidemiology work [10, 17], of which this paper was an important contribution. Powerful tea ….

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