

Meynell G G & Subbiah T V. Antibacterial mechanisms of the mouse gut. I: kinetics of infection by *Salmonella typhi-murium* in normal and streptomycin-treated mice studied with abortive transductants. *Brit. J. Exp. Pathol.* 44:197-208, 1963; and Meynell G G. Antibacterial mechanisms of the mouse gut. II: the role of Eh and volatile fatty acids in the normal gut. *Brit. J. Exp. Pathol.* 44:209-19, 1963.
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Salmonella typhimurium fails to multiply in the normal mouse gut after oral infection because it is inhibited by the fatty acids and low oxidation-reduction potential (Eh) of the caecal contents, both produced by the metabolism of the normal gut flora. This agrees with the observed true division rate and true death rate of the salmonella within the gut, as previously measured with abortive transductants. [The *SCI*® indicates that these papers have been cited together in over 220 publications.]

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April 8, 1987

Although these experiments on the gut contents gave convincing results and were a pleasure to do, I have to admit that they were only a by-product of a long-standing interest in the kinetics of infections of all kinds. On entering medical microbiology, I had noticed, first, that it included innumerable descriptions of specific infections without attempting an account of infection in general; and, second, that microbiologists seemed to assume that, because they could hold a mouse in their hands, it was necessarily easier to analyse it than, say, a distant planet. In fact, the variability of living matter made the contrary just as likely. Indeed, the sheer accessibility of the mouse seemed to concentrate attention on its components to the exclusion of its behaviour as a whole; whereas the remoteness of planets forced early observers to observe them intact,

largely by indirect methods such as the precise measurements of orbits—which turned out to yield results of great general interest. That approach applied to infection would clearly lessen the likelihood of artefacts. Some typical general questions we examined were: why is a host more likely to die, and to die sooner, the more organisms are inoculated; and can the onset of acquired immunity be detected during an infection that is ultimately fatal?^{1,2}

Initially, we had no idea of how fast bacteria multiplied *in vivo* because colony counts only showed the net results of bacterial multiplication and death. This led to the use of nonreplicating genetic markers (either superinfecting phage³ or an abortively transduced gene, as here). These were introduced into the bacteria before inoculation: thereafter, the proportion of marked cells halved in each bacterial generation. Assuming marked and unmarked cells behaved the same *in vivo*, the number of generations occurring in a given time after infection was obtained by comparing the proportions of marked cells recovered from the tissues with that in the dose. The object of the gut papers was, therefore (in my view), to see whether an antibacterial mechanism did exist within the mouse gut that had the properties predicted from the abortive transductants inoculated in the first of the two papers.

Looking back, the general problems of infection still seem as important now as they did three decades ago. As regards true division rates *in vivo*, it should be appreciated that, while the failure of the marker particles to replicate means that the proportion of marked cells halves per generation, it also means that the proportion can decrease so much as to be almost undetectable. It would be useful to find new markers that replicated perhaps 50 percent as fast as their bacterial hosts to allow measurements over more generations. [For a recent paper on intestinal bacteria in animals, see reference 4.]

1. Williams T & Meynell G G. Time-dependence and count-dependence in microbial infection. *Nature* 214:473-5, 1967.
2. Meynell G G & Meynell E. Quantitative aspects of microbiological experiments. *Theory and practice in experimental bacteriology*. Cambridge, England: Cambridge University Press, 1970. p. 173-255.
3. Meynell G G. Use of superinfecting phage for estimating the division rate of lysogenic bacteria in infected animals. *J. Gen. Microbiol.* 21:421-37, 1959.
4. Hirsh D C. Fimbriae: relation of intestinal bacteria and virulence in animals. *Advan. Vet. Sci. Comp. Med.* 29:207-38, 1985.