

## This Week's Citation Classic<sup>®</sup>

Datta N. Transmissible drug resistance in an epidemic strain of *Salmonella typhimurium*. *J. Hygiene* 60:301-10. 1962.  
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This is the first report, from outside Japan, of the conjugative transfer of genetic information for antibiotic resistance between bacteria. During a hospital epidemic, a majority of *Salmonella typhimurium* isolates were sensitive to all antibacterial drugs; but approximately 3 percent were resistant to three unrelated ones, and that multiple resistance was transmissible, in mixed broth culture, to *Shigella sonnei*. (The *SCI*<sup>®</sup> indicates that this paper has been cited in over 140 publications.)

### Early Encounter with Resistance Plasmids

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When, in 1957, I was appointed assistant lecturer in the Department of Bacteriology of the (now Royal) Postgraduate Medical School at Hammersmith Hospital, I was expected to carry out some original research in addition to teaching and doing diagnostic work. It happened that in 1959 there was an outbreak of infection, in both staff and patients, with *Salmonella typhimurium*.<sup>1</sup> For some months, investigating this outbreak put a heavy burden of work on the department. I discussed various research projects with friends, and one (G.G. Meynell) suggested that I should collect *S. typhimurium* cultures during the outbreak and later put them all through a series of tests to show whether the epidemic strain remained stable on passage through a number of human hosts. This I did; antigenic, metabolic, and lysogenic results were uniform, as was the phage type; but, of 309 cultures, 25 were drug-resistant. Some of these were resistant only to streptomycin and were from patients treated with streptomycin. Fifteen were resistant to three drugs, sulphonamides, streptomycin, and tetracycline, a most unexpected finding. No patient had been treated with all three.

Just then, there appeared in the *Journal of Bacteriology*, the first paper<sup>2</sup> on the transfer of multiple drug resistance between enterobacteria, discovered

in Japan (most earlier reports had been published, in Japanese or English, in Japanese journals). A colleague (D.A. Mitchison) drew my attention to this paper; and, as a result, I tested my strains for transfer of resistance, in mixed culture, to a sensitive strain of *Shigella sonnei*. My method did not counter-select against the donor. I simply incubated the resistant salmonella overnight, in broth, with the sensitive shigella, diluted with more broth, incubated again, and plated the culture on MacConkey agar, incorporating streptomycin and/or tetracycline. Resistant shigella colonies were recognized by their colonial appearance, replated, properly identified, and tested for resistance. They had acquired all three resistances of the donor strain. None of the cultures resistant solely to streptomycin transferred resistance; there was one resistant solely to tetracycline, and that resistance was transferred. In each case, the *S. sonnei*, having acquired resistance, could transmit it back to a sensitive *S. typhimurium*. I tried to eliminate the transferable resistance with acriflavine and found, in both treated and control cultures, a proportion (about 0.5 percent of colonies after overnight growth in broth) that had lost all resistances.

My results were similar to those of the Japanese workers, and what exciting results they were! Differences were that, in Japan, the original donors were *Shigella flexneri*, most commonly resistant to chloramphenicol, in addition to sulphonamides, streptomycin, and tetracycline. In the early 1960s, there was much less communication with Japanese scientists than there is now, and their reports of transmissible antibiotic resistance, as well as my own results, were at first treated with some scepticism by microbial geneticists to whom I talked. However, I was sure that I had included all proper controls in my experiments and convinced them by the time my 1962 paper came out in the *Journal of Hygiene*. Had I been more knowledgeable and self-confident, I might have submitted it to a journal with a bigger circulation, perhaps *Lancet* or *Nature*, but the then-editor of the *Journal of Hygiene*, H.J. Bensted, was among my friends, and he helped me with the paper.

Like the Japanese, I concluded that the transferred resistances were carried on a plasmid. Resistance plasmids have since made their presence known in pathogenic bacteria of many species, all over the world, and have provided the basis for DNA cloning, contributing to advances in many areas of biological science, outside bacteriology.<sup>3</sup> For me personally, coming across them so fortunately early meant that I was never again in doubt about an interesting research project.

1. Datta N & Pridie R B. An outbreak of infection with *Salmonella typhimurium* in a general hospital. *J. Hygiene* 58:229-41. 1960. (Cited 35 times.)
2. Watanabe T & Fukasawa T. Episome-mediated transfer of drug resistance in Enterobacteriaceae. I. Transfer of resistance by conjugation. *J. Bacteriology* 81:669-78. 1961. (Cited 250 times.)
3. Berger S L & Kimmel A R, eds. Guide to molecular cloning techniques. (Whole issue.) *Meth. Enzymology* 152. 1987. 812 p.