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This Week's Citation Classic®

Anderson E S. The ecology of transferable drug resistance in the enterobacteria. *Annu. Rev. Microbiol.* **22**:131-80, 1968.
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This was a review of transferable (plasmid-borne) drug resistance, discovered by the Japanese in the shigellae, which cause human bacillary dysentery. Resistance was usually multiple, and all resistances were transferred simultaneously between bacteria by conjugation. [The *SCI*® indicates that this paper has been cited in over 315 publications.]

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Watanabe designated the transferable elements "resistance factors" (R factors), and he postulated the presence of an agent in the linkage group that would mediate the transfer, which he named the "resistance transfer factor" or RTF.[1]

My observations with the antibiotic-resistant *Salmonella typhimurium*, epidemic in calves and man from 1963, revealed R factors different from those in Japan. The strain concerned belonged to phage-type 29 and was predominantly resistant to ampicillin (A), streptomycin (S), sulphonamides (Su), and tetracyclines (T). It transferred A, SSu, and T independently to *Escherichia coli* K12 in overnight crosses.

Further work showed that A and SSu were independent, nonautotransferring resistance plasmids that were mobilised by the RTF, an independent transfer plasmid, which I designated Δ. This was transferred alone with high frequency in overnight crosses, and it also mediated the transfer of plasmids such as A and SSu at much lower frequency and apparently without stable recombination. It recombined stably with T, to form an R factor similar to those discovered by the Japanese.

The independence of the A, SSu, and Δ plasmids suggested to me that they probably existed independently in "wild" bacteria, and I devised a test for this hypothesis: the so-called "triple cross,"[2] in which three bacterial strains are employed. One carries a transfer plasmid only; the second carries a resistance plasmid only; and the third carries neither agent, but is chromosomally resistant to a drug to which the other two are sensitive. After incubation, selection is exercised with the drug corresponding to the resistance plasmid and that to which the first two strains are sensitive. The surviving bacteria are those that have received the resistance plasmid, carried by the transfer plasmid into the third strain, which is already protected by its mutational resistance against the drug finally employed for selection.

This test showed that many wild enterobacterial strains carry transfer plasmids without resistance, while others carry resistance plasmids such as A and SSu but no transfer plasmid. The triple cross established the fundamental independence of the two types of plasmid and also revealed that transfer plasmids (sometimes called "conjugative plasmids") are widely distributed in drug-sensitive bacteria, irrespective of their age. All strains of type 29, isolated before the appearance of drug resistance in the type, carried a Δ-like transfer plasmid. The oldest was isolated in 1947, before the intensive use of antibiotics.

The oldest drug-sensitive *S. typhimurium* I tested in 1967, which carried a transfer plasmid, was isolated in Scotland in 1923. Such strains preceded the advent of antibiotics. They indicate the antiquity of transfer plasmids and establish their basic independence of the resistance plasmids or transposons with which they associate or recombine, once the selective influence of the use of antibiotics has reached a level adequate to ensure contact between the two types of agent. Because they can mediate the transfer of many types of character, they are probably of evolutionary importance in bacteria.[3]

Victoria Hughes and Naomi Datta have recently published two articles based on this work.[4,5]

1. **Watanabe T.** Infectious heredity of multiple drug resistance in bacteria. *Bacteriol. Rev.* **27**:87-115, 1963. (Cited 645 times.)
2. **Anderson E S.** A rapid screening test for transfer factors in Enterobacteriaceae. *Nature* **208**:1016-17, 1965. (Cited 90 times.)
3. ———. Possible importance of transfer factors in bacterial evolution. *Nature* **209**:637-8, 1966. (Cited 30 times.)
4. **Hughes V M & Datta N.** Conjugative plasmids in bacteria of the "pre-antibiotic" era. *Nature* **302**:725-6, 1983.
5. **Datta N & Hughes V M.** Plasmids of the same Inc groups in the Enterobacteria before and after the medical use of antibiotics. *Nature* **306**:616-17, 1983.

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