Drug Resistance in Protozoa

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1. PROTOZOAL INFECTIONS OF HUMANS

Treatment failures have been recorded in the chemotherapy of protozoal diseases almost since such therapy began. Failures may have a number of causes, only one of which is true pathogen resistance to the drug. Perhaps the major obstacle to our comprehension of the problems of drug resistance is our lack of basic understanding of the biology of protozoal infections in humans. Parasites may show reduced sensitivity to chemotherapy because of hidden forms in drug-impermeable areas such as abscesses or the CNS, differences in susceptibility of the various stages of protozoan life cycles, dependence on the host immune response of drug efficacy, individual variations in pharmacokinetics, inadequate dosing, oxygen dependence of some drugs, or simply inherent variations among strains or species of parasites in drug sensitivity. This last factor is especially important for drugs that are effective only when given at or near the maximally tolerated dose.

True drug resistance can be defined as a stable genotypic variant, selected from a normally sensitive population by drug exposure, that has the ability to survive and even multiply in the presence of normally effective drug concentrations. Every population contains individuals having a range of drug sensitivity distributed in a Poisson fashion, and different strains or closely related species may show inherent profound differences in drug sensitivity. These are not examples of true drug resistance, although they may be of considerable clinical importance, any more than gram-negative bacteria can be considered "resistant" to penicillin G. As Peters (1974a) noted, we must differentiate resistance to therapy attributable to drug failure or innate insensitivity from true selected drug resistance. Although our present understanding of drug resistance in
bacteria is far greater than that in protozoa, the advent of successful in vitro culture techniques for most protozoal pathogens may be expected to lead to rapid advances (cf. Jensen, 1983) (vide infra).

1.1. *Toxoplasma gondii*

Treatment failures occur in these infections, but no evidence is available suggesting drug resistance as the cause. Strain differences in sensitivity have been described (Oshima and Hoshino, 1977). It is likely that cyst forms are relatively insensitive to available drugs by virtue of their inaccessability and low metabolic rate. Experimentally induced resistance to sulfonamides (Sanders and Midved, 1971; Lai *et al.*, 1974) and to other drugs (cf. Pfefferkorn and Pfefferkorn, 1978) is of uncertain relevance to human disease.

1.2. *Entamoeba histolytica*

Recent reviews of the chemotherapy of amebiasis indicate that treatment failures are not uncommon in this disease but that no evidence is yet available demonstrating drug-resistant parasites to be the cause (Biagi, 1981; Neal, 1983). Some of the useful drugs have effects that are more or less limited to parasites in tissues or in the intestinal lumen, undoubtedly accounting for some reports of failure (Biagi, 1981). Ameba in abscesses may sometimes be difficult to treat because of poor drug penetration. Biagi (1981) summarized data on local drug concentrations necessary to produce amebicidal effects in different sites. Differences in invasiveness among *E. histolytica* strains may thus cause apparent resistance to metronidazole (Sargeaunt and Williams, 1978; Sargeaunt *et al.*, 1982; Pehrson and Bengtsson, 1983). Other explanations for treatment failures include the insensitivity of cyst stages (Bakshi *et al.*, 1978) and inactivation of drugs (particularly metronidazole) by gut flora (Ralph and Clark, 1978). Species differences in sensitivity also exist (cf. Chacin-Bonilla, 1980) that might lead to assumptions of drug resistance in improperly diagnosed cases.

It has proved difficult to create drug-resistant strains in vitro (Neal, 1983), and currently no proof of true clinical drug resistance is available. A recently developed in vitro model for the assessment of drug sensitivity should aid in defining the extent, if any, of resistance (Cedeno and Krogstad, 1983).

1.3. *Giardia lamblia*

Drug resistance in clinical cases has not been reported. Treatment failures occur but are often cured with a second course of therapy. Optimal dosage schedules still need to be defined that, along with reinfection, may account for the observed failures. An in vitro model for routine susceptibility testing was recently developed (Jokipii and Jokipii, 1980). An isolate from a patient clinically resistant to quinacrine or metronidazole (alone) was shown to be sensitive to these drugs in vitro (Smith *et al.*, 1982), indicating that resistance cannot yet be invoked as an explanation of treatment failures.