【50周年記念特別企画】

Present and Future of Anti–bacterial and Anti–fungal Chemotherapy

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Evidence that attempts to find compounds which would kill microbial pathogens dates back to a number of ancient cultures, i. e. 2500 B. C. However, the "modern era" of antimicrobial therapy began in the early years of the 20 th century with the discovery of arsenicals by Paul Ehrlich, penicillins by Alexander Fleming, the sulfonamides by Gerhard Domagk, and streptomycin by Selman Waksman who coined the word "antibiotic" to refer to these compounds that killed microbes. During the next 50 years the observations of these four men led other investigators to the discovery of many new structural classes of antimicrobial agents which include the chloramphenicols, tetracyclines, macrolides, polymyxins, lincosamides (lincomycin and clindamycin), coumarins (novobiocin), cycloserines, bacitracin and gramicidin, rifamycins, cephalosporins, cephamycins, glycolipids, monobactams, carbapenems, nitrofurans, nitroimidazoles (metronidazole) and the quinolones. Research in the field of anti–fungal chemotherapy developed much more slowly and early agents included the polyenes (amphotericin B and nystatin), nucleosides (flucytosine), azoles, griseofulvin, pimaricin, and more recently the echinocandins. Chemotherapy for Mycobacterial diseases has been even less rewarding, although isoniazid, para–amino salicyclic acid, ethambutol, pyrazinamide capreomycin, ethionamide, and viomycin have been used extensively. Although each of these anti–microbial agents has had much success in the treatment of numerous patients with bacterial or fungal infections, major problems have emerged in the form of anti–microbial resistance to many of these agents in recent years.

Currently, clinicians who care for these patients are often confronted with infections caused by multiply drug resistant organisms. Resistant gram–positive infections include methicillin–resistant staphylococci, peniciilin–resistant pneumococci, macrolide–resistant streptococci and vancomycin–resistant enterococci. Resistant gram–negative coccal infections include penicillin–resistant meningococci and quinolone–resistant gonococci. Also, resistant gram–negative bacilli have occurred in *Enterobacteriacae*, *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., and many other gram–negative rods, particularly *Pseudomonas* spp., *Acinetobacter* spp., *Serratia* spp., and Bacteroides. Invasive fungal organisms, especially *Candida* spp., and *Aspergillus* spp. are beginning to develop resistance to polyenes and azole anti–fungal agents.

We are in need of newer and more effective anti–microbial agents. This work has already begun by looking for new "targets" in both bacterial and fungal cellular function and/or by developing inhibitors of genes involved in microbial pathogenesis. Efforts to combat multi–drug resistant staphylococci and streptococci are really urgent because infections caused by these bacteria increase overall morbidity and mortality. New agents in the streptogramin class (quinupristin–dalfopristin), lipopeptide class (daptomycin), glycopeptide class (oritavancin), ketolide class (telithromycin), and glycylcyclines are designed to combat these infections. Also, new azoles (ravuconazole and posaconazole) as well as new echinocandins are being studied to treat invasive fungal infections.

Those of us who care for patients with infections must encourage the pharmaceutical industry to continue their efforts in antimicrobial discovery.