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A personal glimpse of clinical infectious diseases: 1949-1999

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We have witnessed the advent of the antibiotic era and the development of potent immunization agents in the second half of the 20th century. These remarkable scientific tools enable us to treat and control infectious diseases effectively. Yet the development of microbial resistance to antimicrobial agents and the emergence of new or previously unrecognized infectious diseases continue to challenge the medical and public health professionals. Most ominously, the ill-natured terrorists and mistrustful administrators in certain nations have capitalized on the modern microbial technology to create means for bioterrorism and biological warfare. When will humans ever learn?

Key words: Antibiotics, bioterrorism, emerging infections, vaccinations

This article is a collection of personal thoughts and reminiscences from my professional career of clinical practice in infectious diseases. Portions of this essay were incorporated in an address I delivered to the 15th Annual Meeting of the ROC Infectious Diseases Society at which time the members were so graciously conferred on me the honor of the Life Achievement Award. By no means is this paper intended to be totally objective and scientific, nor is it an in-depth review of infectious diseases in the last half of the 20th century. I emigrated from China to the United States right after my graduation from the West China Union University College of Medicine and my postgraduate medical career began in the United States. Therefore the descriptions of my reflections in clinical medicine are drawn almost entirely from my experiences in the United States. With humility and a thankful heart, I owe much to my family for their loving support, to my mentors who taught me the skills, and to my many colleagues, students and patients who helped make my chosen career most enjoyable and pleasant.

Antimicrobial Therapy and Bacterial Resistance

Penicillin G has been celebrated as the first antibiotic of the antibiotic era. However, the term "antibiosis" appeared in medical literature at Pasteur's time in the 1870s. In 1939, Rene Dubos reported the isolation of gramicidin and tyrocidin from a soil bacillus with bactericidal activity against gram-positive organisms [1-3]. Due to its toxicity, gramicidin was never utilized clinically for systemic use but it is highly effective as a topical antimicrobial for treating wound and skin infections. Dubos' work on gramicidin stimulated Howard Florey and Ernest Chain to revive clinical research on penicillin. Penicillin was first discovered by Alexander Fleming in 1928 but remained clinically unrecognized for more than a decade [4]. It was the Oxford group headed by Florey who did the clinical trials and introduced penicillin to medical use. Before the advent of penicillin, Gerhard Domagk had performed laboratory and clinical studies of Prontosil (sulfonamide). He found prontosil had activities against streptococcal infections and introduced it for clinical use in 1935 [5]. These major discoveries were followed quickly by the mushrooming growth of different classes of antimicrobial agents, streptomycin, tetracyclines, macrolides, chloramphenicol and others that were added to the antibiotic armamentarium in the 1940s and 1950s and beyond (Table 1). Many of these antibiotic discoverers and other biomedical scientists were awarded Nobel Prizes (Table 2).

Table 1. Era of antimicrobials with examples

Year	Antimicrobial agent
1940s	Penicillin G; streptomycin
1950s	Erythromycin; tetracyclines
Early 1960s	Methicillin; ampicillin
Late 1960s	Cephalosporins; aminoglycosides
1970s	More penicillins and cephalosporins
Early 1980s	Third generation cephalosporins; carbapenems; monobactam
Late 1980s	Quinolones
1990s	New macrolides-azithromycin, clarithromycin; more quinolones, streptogramins, oxazolidinone

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Table 2. Nobel laureates with contributions to infectious diseases

Year	Name	Contributions
1939	Gehard Domagk	Discovery of antimicrobial effects of prontosil which led to the developments of sulfa drugs.
1945	Alexander Fleming Howard W. Florey Ernest B. Chain	They shared the Nobel Prize for the discovery of penicillin and its curative effects in various infectious diseases. This opened up the antibiotic era.
1952	Selman A. Waksman	Discovery of streptomycin, the first antibiotic effective against tuberculosis.
1954	John F. Enders Thomas H. Weller Frederick C. Robbins	They shared the Nobel Prize for their discovery of growing poliomyelitis viruses in tissue culture. This opened up the development of poliomyelitis vaccines.
1976	Baruch S. Blumberg Carlton Gajdusek	For their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases. Blumberg discovered the "Australian antigen" which became the hepatitis B surface antigen. Gajdusek discovered Kuru-spongiform encephalopathy.
1997	Stanley B. Prusiner	For his discovery of prions: a new biological principle in understanding transmissible encephalopathies.

In 1944, when I was a third-year medical student at the West China Union University, I had the privilege of participating in the use of penicillin G to treat several patients with skin and soft tissues infections, staphylococcal abscesses and carbuncles. Dr. Leslie G. Kilborn, then the Dean of the College of Medicine and Chairman of the Department of Pharmacology, returned from his sabbatical to Canada with some 60,000,000 units of penicillin G for clinical trial. After surgical incision and drainage of the abscesses, administration of only a few thousand units of penicillin G to those patients was uniformly effective in achieving a cure. I recall that 60,000,000 units of penicillin G lasted us several months rather than being the few days' supply it is in current medical usage!

When penicillin was first introduced into clinical usage, over 90% of the *Staphylococcus aureus* strains were sensitive to penicillin G. Not long after the introduction of penicillin G into clinical use, medical literature began to report the emergence of penicillin resistant strains of *S. aureus* which produced penicillinase that inactivated the antibiotic [6]. With the spread of penicillin resistance to other *S. aureus* isolates by the late 1940s and early 1950s, staphylococcal infections became a major infectious disease problem in communities as well as in hospitals. The development of semisynthetic penicillinase-resistant penicillins — first methicillin, followed by isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin) and nafcillin — in the early 1960s was helpful in temporarily solving the penicillin-resistant *S. aureus* problem. But as early as 1961, methicillin-resistant *S. aureus* (MRSA) started to appear. The emergence of MRSA [7] once again put us in a therapeutic dilemma in regard to staphylococcal infections. Glycopeptides (vancomycin and teicoplanin) become the main antibiotics for combating MRSA and coagulase negative staphylococci (MRSE). However, vancomycin insensitive *S. aureus* (VISA) with MIC 8 μg/mL was isolated from the wound of a 4-month boy in Japan in 1998. Other VISA strains were soon isolated also in the United States [8]. Truly vancomycin-resistant *S. aureus* with MIC more than 16 μg/mL has not been reported as of yet but anticipating its possible arrival is certainly worrisome. The recent approval of streptogramin antibiotic [9] and oxazolidinones [10] may help us in treating the glycopeptide insensitive and/or resistant organisms. Sufficient clinical experiences from the utility of these new agents are limited and their impact in clinical medicine remains to be elucidated.

Other species of bacteria, both gram-positive and gram-negative organisms, are also developing antibiotic resistance [11]. Multiply drug resistant enterococci including resistance to vancomycin have emerged in the last few years and have become common organisms responsible for nosocomial infections [12]. Penicillin and multi-drug-resistant pneumococci are now a global problem [13]. Certain serotypes of pneumococci such as 6B and 23F appear to have the highest rates among the resistant isolates. With a more complicated cell wall structure than the gram-positive organisms, the emergence of resistant enterobacteriaceae presents another challenge in clinical practice, particularly among nosocomial infections in Intensive Care Units (ICUs). The advent of the third-generation cephalosporins in the early 1980s with good broad spectrum activity against the enterobacteriaceae opened up a new page in clinical medicine for serious gram-negative infections in hospitalized patients. However, the production of extended spectrum beta-lactamases (ESBLs) by resistant organisms following the general

usage of these potent cephalosporins has curtailed the effectiveness of these broad-spectrum cephalosporins. The Centers for Disease Control and Prevention (CDC) reported in 1998 that ceftazidime-resistant *Klebsiella pneumoniae* reached 10.7%, and ceftazidime-resistant *Escherichia coli* reached 3.2% in the ICUs of US hospitals with higher prevalence in teaching institutions. ESBL-producing organisms can transfer the plasmid to a variety of bacterial strains and even to different bacterial genera leading to outbreaks of nosocomial infections. Risk factors such as the use of mechanical ventilation, placement of percutaneous devices, prolonged hospital stay of morbid patients and frequent use of antibiotics particularly ceftazidime and aztreonam contribute to the emergence of ESBLs in gram-negative organisms. Other than the production of ESBLs, organisms of *E. coli* and *K. pneumoniae* groups can develop resistance by chromosomal production of *ampC* enzymes [14]. Organisms such as *Enterobacter*, *Serratia*, *Pseudomonas*, *Citrobacter* and indole-positive *Proteus* species that produce *ampC* are important nosocomial pathogens [15]. Aside from producing beta-lactamases, other mechanisms, either acting singly or in combination cause the bacteria to be resistant against various antimicrobials. Alteration of the porins and permeability of the outer membranes, decreased uptake through the cytoplasmic membrane, and active efflux to transport the drug out across the cytoplasmic membrane are important mechanisms in limiting and lowering the concentration of antimicrobials reaching the treatment targets of invading pathogens [16].

The Impact of Controlling Infectious Diseases Through Vaccination

Benjamin Franklin's famous proverb "An ounce of prevention is worth a pound of cure" certainly is a guidepost in medical practice. The success of implementing immunization programs for preventing many infectious diseases and improving the health of the general public in the past five decades is one of the most gratifying experiences of my medical career. I have selected a few examples for discussion here.

Smallpox

The British physician, Edward Jenner is credited with developing the smallpox vaccine in 1796. The introduction of cowpox vaccine (note that *vacca* in Latin means cow) had greatly reduced, although not eradicated, the mortality and morbidity of smallpox. During 1900 to 1904, an average of 48,164 cases and 1528 deaths caused by both variola major (severe) and variola minor (mild) were reported annually in the United States [17]. I recall that throughout my childhood years and medical school days, I did occasionally see cases of smallpox patients. Variola major ceased to occur in the United States in 1949. In the year of 1977, the World Health Organization (WHO) declared that the last recorded naturally caused smallpox case, a Mr. Ali Maalim, occurred in Somalia, Africa. Smallpox has been globally eradicated [18].

Poliomyelitis

Being a virologist, it was exciting in my professional career to personally witness the developments of several highly potent vaccines to control viral diseases. During the period of 1951 to 1954, there were an average of 16316 paralytic poliomyelitis cases and 1879 deaths from poliomyelitis were reported each year in the United States [19]. The inactivated Salk polio vaccine was licensed in the United States in 1955. This was followed by the introduction of the live attenuated Sabin vaccine in 1958. The incidence of poliomyelitis declined precipitously following the introduction of these vaccines. The last documented case of poliomyelitis from indigenous transmission of wild type of poliovirus in the United States occurred in 1979. Thereafter, only vaccine-associated or imported poliomyelitis cases were recorded. Wild-type poliomyelitis illnesses were declared to be eliminated from the Western hemisphere in 1991 [20]. Most recently, the Advisory Committee of Immunization Practice has recommended that the use of the live attenuated vaccine be discontinued and only the inactivated vaccine is to be used for primary poliomyelitis immunization in the United States.

Measles, mumps and rubella

Three live attenuated vaccines, the measles vaccine was licensed in the United States in 1963, the mumps vaccine in 1967 and the rubella vaccine in 1969. In a combination preparation, these three agents become one of the basic vaccines for children. Most school districts in the United States require certification that children have received these vaccines prior to enrollment in public schools. The measles vaccine was derived from the Edmonton strain of measles which was isolated from a pediatric patient at the Boston Children's Hospital and attenuated by passage in tissue cultures. The mumps vaccine was from the Jerry Lynn strain of mumps virus. This isolate came from the daughter of the mumps vaccine developer, Dr. Maurice Hilleman of the Merck Company. The RA/27 strain of rubella virus was from a rubella abortus, the 27th specimen. With the advent of these three live attenuated vaccines, usually given in combination as one dose by intramuscular injection,

the incidence of these three childhood diseases and their serious complications such as encephalitis and congenital cardiac anomalies have dramatically decreased.

Hepatitis B

Among all agents causing liver diseases, the hepatitis B virus (HBV) has been recognized as one of the most important agents by virtue of its potential to result in a chronic infection and a carrier state. Hepatic cirrhosis and hepatocellular carcinoma are associated with chronic hepatitis. Prior to the development of the HBV vaccine, the HBV carrier rate in Taiwan was in the range of 15% to 20%. In Taiwan, a nation-wide HBV vaccination program was launched in 1984. By 1994, the HBV carrier rate in children dropped from 10% to less than 1% [21] and the incidence of hepatocellular carcinoma in children also declined significantly [22].

Haemophilus influenzae type b (Hib) infections

Among all capsular types of *Haemophilus influenzae* organisms, Hib is the most virulent type associated with invasive diseases including meningitis, epiglottitis and bacteremia. Before the introduction of an effective vaccine, Hib was the most common cause of bacterial meningitis in children. Meningitis and other invasive Hib infections occur most commonly in children between 3 months to 3 years of age. With introduction of the conjugated vaccine in 1988 in the United States, the incidence of invasive-Hib disease has declined by 95% in infants and young children [23].

Emergence of Novel Infections

During the span of my medical career, I have seen the emergence of a number of new infectious diseases. In the first issue of the journal *Emerging Infectious Diseases* published in January 1995, Dr. David Satcher who was the Director of the Centers for Disease Control and Prevention, listed 22 major etiologic agents of infectious diseases identified since the year of 1973 [24]. I have listed a number of agents isolated and identified since 1950 (Table 3). Many of these agents I have had the privilege of working on in my research laboratories. Based on my own experiences in caring for these patients infected with these agents, I would like to make some personal remarks on a few of them because of their historical interest to the medical communities in Taiwan.

Legionella pneumophila

In September 1976, I was consulted to see a patient who developed pneumonitis after renal transplantation at the University of Kansas Medical Center. Soon thereafter, two more similar cases occurred among other renal transplant patients. Unfortunately, all three patients died. No bacterial or viral pathogens were isolated from these patients in our clinical laboratories. This unknown illness forced us to suspend our renal transplant program for several months. When the *L. pneumophila* organism was identified and a serologic test was developed a year later [25], we were able to confirm that our expired transplant patients did have Legionnaires' disease. During my 1984 trip to Taiwan,

Table 3. Selected list of major infectious disease etiologic agents

Year	Agent	Disease
1954	Measles virus	Measles (Rubeola)
1956	Rhinoviruses	Common cold
1956	Cytomegelovirus	Cytomegalovirus diseases
1958	Varicella-Zoster virus	Chickenpox, herpes zoster
1962	Rubella virus	German measles (Rubella)
1964	Epstein-Barr virus	Infectious mononucleosis, Burkitt lymphoma
1965	Hepatitis B virus	Acute and chronic hepatitis
1973	Hepatitis A virus	Acute hepatitis
1973	Rotavirus	Major cause of infantile diarrhea worldwide
1977	*Legionella pneumophila*	Legionnaires' disease
1977	Hantaan virus	Hemorrhagic fever with renal syndrome
1981	Staphylococcus exotoxin	Toxic shock syndrome
1982	*E. coli* O157:H7	Hemorrhagic colitis, hemolytic uremic syndrome
1982	*Borrelia burgdorferi*	Lyme disease
1983	Human immunodeficiency virus (HIV)	Acquired immunodeficiency syndrome (HIV/AIDS)
1983	*Helicobacter pylori*	Gastric ulcers
1988	Human herpesvirus-6	Roseola subitum
1989	Hepatitis C	Parenterally transmitted hepatitis
1992	*Bartonella henselae*	Cat-scratch disease, bacillary angiomatosis
1993	Hantavirus	Hantavirus pulmonary syndrome

I brought several charcoal yeast extract culture plates and some diagnostic agents for *L. pneumophila* to the Veterans General Hospital (VGH) in Taipei. At one of our teaching rounds, the staff at VGH and I saw a patient with pulmonary infiltrates and we were able to confirm the first recognized case of Legionnaires' disease in Taiwan [26].

Acquired immunodeficiency syndrome (AIDS)

Two articles published back to back in the December of 1981 issue of the *New England Journal of Medicine* described the occurrence in the late 1970s of community acquired *Pneumocystis carinii* pneumonia in previously healthy homosexual men residing in New York and in California [27,28]. These two reports announced the arrival of the era of AIDS. Almost 20 years later, in spite of many notable advances in our scientific understanding and management of this dreadful disease, the hope of finding a cure and an effective control program for this global human suffering is not in sight. Initially, the medical community thought some sort of unknown immunosuppressive disorder in these patients led them to develop life-threatening opportunistic infections and/or an aggressive form of Kaposi's sarcoma [29]. I recall that the first case of AIDS patient discussed at the Medicine Grand Rounds at the University of Kansas Medical Center was presented by the staff from the Division of Clinical Immunology. When the etiologic agent was isolated, identified in 1983 and named Human Immunodeficiency Virus (HIV) in 1984 [30], HIV/AIDS was classified as an infectious disease. During my 1984 visit to Taiwan, I was informed that there were no reported clinical cases of AIDS in ROC. A small number of hemophiliacs who had received factor VIII blood products, were known to be HIV seropositive. During my short 2-week visit to Taiwan in January 2000, I was presented with a total of five advanced cases of AIDS patients. The most common medical complication they suffered was reactivation of pulmonary tuberculosis!

Epidemic influenza

All of us who practice infectious diseases can recall the 1918 to 1919 pandemic of epidemic influenza with 20,000,000 deaths worldwide. Since the influenza virus was not isolated until 1933, the nature of the pandemic virus was not defined. From serological studies on individuals who survived the 1918 to 1919 pandemic, the virus was found to be antigenically related to the "swine flu". More recently, at the Armed Forces Pathology Institute, using polymerase chain reaction (PCR) probing on the paraffin blocks of lung tissues from soldiers who had died of influenza during the First World War, the agent was determined to be a variant of H1N1 influenza A virus. Further proof came from the identification of similar RNA genomic sequences of the virus from the lung of a victim buried deep in snow since 1918 in Alaska [31]. In 1976, the occurrence of "swine flu" cases in a military training camp in New Jersey with evidence of direct human to human transmission created a national crisis in the United States. In the fall of 1976, a national immunization program was put into effect to prevent the possible occurrence of an epidemic. However, the immunization program was soon aborted after the appearance of increased incidence of Guillain-Barré syndrome in those who received the vaccine. The good news was that the "swine flu" epidemic did not materialize as anticipated. Avian influenza virus has never been shown to infect humans directly. Yet in 1997, the outbreak of H5N1 influenza A virus in Hong Kong was shown to have infected some 18 patients with six deaths [32]. This led to slaughtering more than 1,000,000 chickens leaving Hong Kong residents with no chickens with which to celebrate the Chinese Lunar New Year! Scientifically, this incident has profound implications and put the public health officials and virologists on alert for the possible occurrence of a future global pandemic caused by a new influenza virus.

Bioterrorism and Biological Warfare

The use of microorganisms and toxins as weapons of warfare has been described throughout history [33,34]. Bioterrorism and biological warfare against civilians have become very common discussion topics for books, movies and national security planing [35]. The First National Symposium on Medical and Public Health Response to Bioterrorism was held in Arlington, Virginia in February, 1999 with representatives from 46 of the 50 states from the United States and 10 countries attending. Production of large quantities of pathogenic microorganisms does not require much scientific sophistication nor very elaborate and

Table 4. Impact of biological warfare - terrorism

Disease	Infective dose	Dead	Incapacitated
If 50 kg of each of the following agents aerosolized upwind in a city of 500,000 population:			
Anthrax	8000	95000	125000
Brucellosis	10	500	125000
Q fever	1	150	125000
Smallpox	10	?	Large number
Tularemia	10	30000	125000
Typhus	?	19000	85000

expensive facilities. Delivery of the biological weapon is relatively easy; even a single individual can carry the pathogenic cultures into a country or a city without being detected.

Many species of bacteria or viruses can be used for biological warfare purposes. The candidates most often mentioned include anthrax, brucella, and smallpox. Estimates on the number of casualties on patients exposed to biological attacks are staggering [33,34] (Table 4). An outbreak of anthrax occurred in 1979 in people who lived or worked in a narrow zone of an area about 4 km downwind of a Soviet military microbiologic facility. At least 77 cases with 66 deaths occurred, constituting the largest documented incident of inhalation anthrax in history. In 1992, the USSR government admitted that the epidemic was caused by an accidental release of anthrax spores from the facility which was part of an offensive biologic weapons system. Many of the victims had inhalation anthrax pneumonia secondary to fatal disseminated anthrax septicemia [36].

Since smallpox was declared eradicated globally in 1978, the WHO Committee on Orthopoxviruses recommended in 1996 to the World Health Assembly (WHA) that all live smallpox virus stocks stored in every member country's laboratories be destroyed. The last two countries, Russia and the United States, were supposed to destroy their smallpox virus stocks by 1999. However, a defecting deputy director of the Soviet Union's bioweapons program reported that the Soviet Union had set out as early as 1980s to weaponize smallpox virus. A facility capable of producing 80 to 100 tons of smallpox virus per year had been established under the auspices of the Soviet Union military facilities [37]. In 1999, the United States and Russia, completely reversed their official positions on destroying the smallpox virus stocks arguing that the virus was urgently needed for research purposes. Ironically, Dr. David A. Henderson, the individual who made the greatest contribution to eradicating smallpox globally, is now the most vocal leader warning us of its possible use as a biological weapon [38].

Epilogue

Looking back over the past half century of my medical career, I have been most fortunate to welcome the advent of the antibiotic era which gives us the tools to treat infectious diseases effectively. The development of potent vaccines has successfully prevented and reduced many serious crippling illnesses particularly in children. On the other hand, the emergence of newly recognized infections continues to challenge us. In this high technology age, the various means of rapid communication, both in air travel and in electronic devices, have brought the world closer than ever before. No single population group can exist comfortably without being affected by another group who has medical problems. I recall that some 20 years ago, the first medical delegation from the Peoples' Republic of China (PRC) toured the United States of America and paid a visit to Kansas City. The leader of the delegation whom I had not seen for over 30 years, was my schoolmate at the West China Union University College of Medicine. He asked me what medical specialty I was practicing. I told him that I was in charge of the Division of Infectious Diseases at the University of Kansas Medical Center. He showed amazement and remarked that infectious diseases such as cholera, typhoid fever and venereal diseases were already well under control or "eradicated" in the PRC, so why would a developed country such as the United States would need someone like me to practice infectious diseases? In the twilight years of my medical career, after 50 years as an academic physician, I find that the field of infectious diseases remains not under control or "eradicated", and it has become even more complex than when I first started. All kinds of challenging problems exist for the next generation of biomedical scientists to explore!

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References

1. Dubos RJ. Bactericidal effect of an extract of a soil bacillus on gram-positive cocci. Proc Soc Exp Biol Med 1939;40:311-4.
2. Dubos RJ. Studies on a bactericidal agent extracted from a soil bacillus. II. Protective effect of the bactericidal agent against experimental pneumococcus infections in mice. J Exp Med 1939;70:11-7.
3. Dubos RJ, Cattaneo C. Studies on a bactericidal agent extracted from a soil bacillus. III. Preparation and activity of a protein-free fraction. J Exp Med 1939;70:249-56.
4. Fleming A. The antibacterial action of cultures of a *Penicillium*, with special reference to their use in the isolation of *B. influenzae*. Brit J Exper Pathol 1929;10:226-36.
5. Domagk G. Ein Beitrag zur Chemotherapie der Bakteriellen Infektionen. Dtsch med Wschr 1935;61:250-2.
6. Spink WW, Ferris V. Quantitative action of penicillin inhibitor from penicillin-resistant strains of staphylococci. Science 1945; 102:221-3.
7. Barber M. Methecillin-resistant staphylococci. J Clin Pathol 1961;14:385-93.
8 Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J Antimicrob

Chemother 1997;40:135-6.
9 Qadri SM, Ueno Y, Abu Mostafa FM, Halim M. *In vitro* activity of quinupristin/dafopristin, RP59500, against gram-positive clinical isolates. Chemotherapy 1997;43:94-9.
10. Diekema DI, Jones RN. Oxazolidinones: a review. Drugs 2000; 59:7-16.
11. Neu HC. The crisis in antibiotic resistance. Science 1992;257: 1064-73.
12. NNIS (National Nosocomial Infections Surveillance). NNIS Semiannual Report. Atlanta, GA, US Department of Health & Human Services, 1998.
13. Campbell GD Jr, Silberman R. Drug-resistant *Streptococcus pneumoniae.* Clin Infect Dis 1998;26:1188-95.
14. Papanicolaou GA, Medeiros AA, Jacoby GA. Novel plasmid-mediated s-lactamase (MIR-1) conferring resistance to oxyimino- and alpha-methoxy β-lactams in clinical isolates of *Klebsiella pneumoniae.* Antimicrob Agents Chemother 1990; 34:2200-9.
15. Sanders CC. Beta-lactamases of gram-negative bacteria: new challenges for new drugs. Clin Infect Dis 1992;14:1089-99.
16. Kaye KS, Fraimow HS, Abrutyn E. Pathogens resistant to antimicrobial agents: epidemiology, molecular mechanisms, and clinical management. Infect Dis Clin N Am 2000;14:293-319.
17. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva, Switzerland: World Health Organization, 1988.
18. World Health Organization. The Global Eradication of Smallpox. The final report of the Global Commission for the Certification of Smallpox Eradication. December, 1979. Geneva; 1980.
19. CDC. Reported incidence of notifiable diseases in the United States, 1960. MMWR 1961;9.
20. CDC. Certification of poliomyelitis eradication: the Americas, 1994. MMWR 1994;43:720-2.
21. Chen HL, Chang MH, Hsu HY, Lee PI, Lee CY, Chen DS. Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. JAMA 1996;276: 906-8.
22. Chang MH, Chen CJ, Lai MS, Hsu HM, Hsu HM, Wu TC, Kong MS, Liang DC, Sau WY, Chen DS. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. N Engl J Med 1997;336:1855-9.
23. American Academy of Pediatrics. 1997 Red Book: Report of the Committee on Infectious Diseases, 24th ed. Elk Grove Village, IL: American Academy of Pediatrics, 1997:220-31.
24. Satcher D. Emerging infections: getting ahead of the curve. Emerg Infect Dis 1995;1:1-9.
25. McDade JE, Shepard CC, Fraser DW, Tsai TR, Redus MA, Dowdle WR. Legionnaires' disease: isolation of a bacterium and demonstration of its role in other respiratory disease. N Engl J Med 1977;297:1197-203.
26. Liu YC, Cheng DL, Shi FW, Huang WK, Wang JH. Legionnaires' disease: a case report. J Formos Med Assoc 1985; 84:1180-5.
27. Gottlieb MS, Schroff R, Schanker HM, Weismam JD, Fan PT, Wolf RA, Saxon A. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men. N Engl J Med 1981:305:1425-30.
28. Masur H, Michelis MA, Greene JB, Onorato I, Stouwe RA, Holzman RS, Wormser G, Brettman L, Lange M, Murray HW, Chuningnam-Rundles S. An outbreak of community-acquired *Pneumocystis carinii* pneumonia. N Engl J Med 1981:305:1431-8.
29. Durack DT. Opportunistic infections and Kaposi's sarcoma in homosexual men. N Engl J Med 1981;305:1465-7.
30. Streicher HZ, Reitz MS, Gallo RC. Human immunodeficiency viruses. In: Mandell GL, Bennett J, Dolin R, eds. Principles and Practice of Infectious Diseases. 5th ed. Philadelphia: Churchill Livingstone, 2000:1874-87.
31. Reid AH, Fanning TG, Hultin JV, Taubenberger JK. Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene. Proc Natl Acad Sci USA 1999;96:1651-6.
32. Mounts AW, Kwong H, Izurieta HS, Ho Y, Au T, Lee M, Buxton Bridges C, Williams SW, Mak KH, Katz JM, Cox NJ, Thompson WW, Fukuda K. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. J Infect Dis 1999;180:505-8.
33. Christopher GW, Cieslak TJ, Pavin JA, Eitzen EM Jr. Biological warfare: a historical perspective. JAMA 1997;278:412-7.
34. Franz DR, Jahring PB, Friedlander AM, McClain DJ, Hoover DL, Bryne WR, Pavlin JA, Christopher GW, Eitzen EM Jr. Clinical recognition and management of patients exposed to biological warfare agents. JAMA 1997;278:399-411.
35. Atlas RM. The medical threat of biological weapons. Crit Rev Microbiol 1998;24:157-68.
36. Abramosa FA, Grinberg LM, Yampolskaya OV, Walker DH. Pathology of inhalation anthrax in 42 cases from the Sverdlosk outbreak of 1979. Proc Natl Acad Sci USA 1993;90:2291-4.
37. Herderson DA. Smallpox eradication: a saga of triumph and betrayal. Infect Dis in Clin Practice 1999;8:445-8.
38. Henderson DA, Inglesby TV, Barlett JG, Ascher MS, Eitzen E, Jaberling PB, Haner J, Layton M, McDade J, Osterholm MT, O'Toole T, Parker G, Perl T, Russell PK, Tonat K. Smallpox as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. JAMA 1999;281:2127-37.