ANTIBIOTICS, SURVEY

1. Introduction

Antibiotics are chemical substances produced by microorganisms and other living systems that in low concentrations are capable of inhibiting the growth of bacteria or other microorganisms. This inhibitory effect can be *in vitro* or *in vivo*. Antibiotics having both *in vivo* activity and low mammalian toxicity have been extremely valuable in treating infectious diseases. There are >16,500 antibiotics produced by microorganisms that have been reported in the scientific literature, ~90% of which have been characterized and have had molecular structures assigned (1,2). These microbial metabolites range from the very simple to extremely complex, but most antibiotics are in the 300–800 mol wt range. Fosfomycin is an example of a clinically used antibiotic with only three carbon atoms and a molecular weight of only 138. Although with this simplicity of chemical structure, it is highly improbable that any synthetic chemist or any combinatorial chemistry system would have created such a structure without the prior knowledge of the structure isolated from the microorganism. The structure is simple, but has two asymmetric carbon centers as part of an epoxide with an attached phosphonic acid group. This illustrates the great value of screening microbial metabolites and other natural products for new antibiotics and other pharmaceutical drugs. Many thousands of semisynthetic variations of the naturally occurring antibiotics have been prepared. Only relatively few (~200) have become commercial products for human and veterinary uses.

Microorganisms producing antibiotics include antinomyces, fungi, bacteria, and algae. Marine organisms, eg, sponges and soft corals, have also been found to produce antibacterial, antifungal, and antitumor antibiotics (3,4). In some cases, symbionic microorganisms, eg, algae may, be responsible for the antibiotic production noted in the higher life forms. Terrestrial plants have also been found to produce a large number of antibiotic-like substances (1), but none of these have had a significant place in treating systemic bacterial or fungal infections in humans.

The mechanism of action of a number of antibiotics with regard to the inhibition of bacteria, fungi, or other organisms, has been established. The more common mechanisms include inhibition of bacteria cell-wall biosynthesis, inhibition of protein, RNA, or DNA synthesis, and damaging of membranes (5,6). Cell-wall biosynthesis is a target present in bacteria, but not in mammalian cells. Thus the β-lactams, which are very effective against bacteria, are relatively nontoxic to humans. In contrast, antibiotics that damage DNA, like adriamycin, are relatively toxic to both types of cells. However, adriamycin, which was found to be more toxic to rapidly proliferating tumor cells than to most normal cells with slower turnover rates, shows significant selectivity against tumor cells to find clinical application as an antitumor agent (5,6).

2. History

Antibiotics were used in folk medicine at least as early as 2500 years ago when the Chinese reported the medicinally beneficial effects of moldy bean

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curd. Evidence for some type of tetracycline antibiotic usage by the Sudanese–Nubian civilization (350 AD) was reported in 1980 (7). Fluorescent areas in human bones from this era were observed that were identical in location and characteristics to modern bone from patients treated with tetracyclines. Identification of tetracycline in the ancient bones was further substantiated by fluorescence spectrum measurements and microbiological inhibition studies (8).

One of the most profound developments in the history of modern medicine has been the discovery of antibiotics to control infections. The realization that microbial products could cure infectious diseases spanned ∼65-years of discoveries (9). One of the first modern scientific demonstrations was the observation by Louis Pasteur in 1877 that common bacteria inhibited the growth of a pure anthrax culture. Other observations followed. Then in 1928 it was noted by Alexander Fleming that a culture of a green *Penicillium* species inhibited the growth of bacteria on an agar plate. In 1932, a paper was published on the use of the penicillin preparation as a topical agent for treating infected wounds. But, it was not until 1940 that a systematic investigation of antibacterial substances was made along with a reinvestigation of the properties of penicillin. A stable dry powder was prepared from fermentations of the *Penicillium* that possessed strong antibacterial properties and the clinical utility of penicillin, which was shown to be highly effective against bacterial infections yet nontoxic to animals, was clearly visible.

In 1939, the isolation of a mixture of microbial products named tyrothricin from a soil bacillus was described. Further investigation showed this material to be a mixture of gramicidin and tyrocidine. In rapid succession, the isolation of actinomycin (1940), streptothricin (1942), streptomycin (1943), and neomycin (1949), produced by *Streptomyces* species, were reported and in 1942 the word antibiotic was introduced. Chloramphenicol, the first of the so-called broad spectrum antibiotics having a wide range of antimicrobial activity, was discovered in 1947. Aureomycin, the first member of the commercially important tetracycline antibiotics, was discovered in 1948.

The number of naturally occurring antibiotics increased from ∼30 known in 1945, to 150 in 1949, 450 in 1953, 1200 in 1960, 10,000 by 1990, and ∼16,500 by 2005 (1,10). Table 1 lists the years of historical importance to the development of antibiotics used for treatment in humans. Most of the antibiotics introduced since the 1970s have been derived from synthetic modifications of the of the β-lactam antibiotics.

3. Nomenclature

Antibiotics, and all other marketed drug products, are identified by three different types of names: (*1*) a chemical name based on standard rules of chemical nomenclature, (*2*) a generic (nonproprietary) name that is relatively short and follows a systematic procedure of describing a compound structure-type and utility, and (*3*) a trade name that is given by the manufacturer to distinguish it from competitive products. Some of the antibiotics discovered prior to 1961, when the U.S. adopted names (USAN) program started, had received many different names in the chemical literature. The USAN program is a specifically organized

effort in the United States directed to producing simple and useful nonproprietary names for drugs, while the drug is still in its investigational stage (11). Most of the antibiotics reported in literature are not of commercial interest and are not given generic names. If the chemical name is too complex, a trivial (nonsystematic or semisystematic) name is often assigned by the discoverer. For industrial organizations, these names usually appear as alphanumeric coded identifiers, such as LL-F28249α, given the generic name of nemadectin, when the commercial potential became apparent (12).

A marketed antibiotic's generic name is usually preferred because it is simpler and easier to remember. Tetracycline [60-54-8], is an example:

chemical name	4-(dimethylamino)-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3, 6,10,12,12*a*-pentahydroxy-6 methyl-1,11-dioxo-2-naphthacenecarboxamide
generic name	tetracycline
trade names	Achromycin (Lederle), Panmycin (Upjohn), Sumycin (Squibb), Tetracyn (Pfizer), Tetrex (Bristol), etc.

4. Classification of Antibiotics

Antibiotics have a wide diversity of chemical structures and range in molecular weight from near 100 to >13,000. Most of the antibiotics fall into broad structure families. A chemical classification scheme for all antibiotics has been difficult because of the wide diversity and complexity of chemical structures. The most comprehensive scheme may be found in Reference 13. Another method of classifying antibiotics is by mechanism of action (5,6). However, the modes of action of many antibiotics are still unknown and some have mixed modes of action. Usually within a structure family, the general mechanism of action is the same. For example, of the β-lactams having antibacterial activity, all appear to inhibit bacterial cell-wall biosynthesis.

A chemical classification of some of the commercially more important antibiotic families that is generally consistent with the schemes of References 2 and 13 is given here.

4.1. Aminoglycosides. Antibiotics in the aminoglycoside group characteristically contain amino sugars and deoxystreptamine or streptamine. This family of antibiotics has frequently been referred to as aminocyclitol aminoglycosides. Representative members are streptomycin, neomycin, kanamycin, gentamicin, tobramycin, and amikacin. These antibiotics all inhibit protein biosynthesis.

4.2. Ansamacrolides. Antibiotics in the ansamacrolide family are also referred to as ansamycins. They are benzenoid or naphthalenoid aromatic compounds in which nonadjacent positions are bridged by an aliphatic chain to form a cyclic structure. One of the aliphatic–aromatic junctions is always an amide bond. Rifampin is a semisynthetically derived member of this family and has clinical importance. It has selective antibacterial activity and inhibits RNA polymerase.

4.3. β-Lactams. All β-lactams are chemically characterized by having a β-lactam ring. Substructure groups are the penicillins, cephalosporins, carbapenems, monobactams, nocardicins, and clavulanic acid. Commercially, this family is the most important group of antibiotics used to control bacterial infections in humans. The β-lactams act by inhibition of bacterial cell-wall biosynthesis. Most commercial antibiotics in this family are prepared by semisynthetic methods that involve acylations of the fermentation derived 6-aminopenicillinic acid or 7-aminocephalosporanic acid. Azetreonam, which is a monobactam antibiotic in the β-lactam family, is prepared by total synthesis.

4.4. Chloramphenicol. Only chloramphenicol and a few closely related analogues fall into this group. Chloramphenicol, a nitro benzene derivative of dichloroacetic acid, inhibits protein biosynthesis.

4.5. Glycopeptides. Vancomycin, avoparcin, and teicoplanin are examples of glycopeptide antibiotics. This family has cyclic peptide structures and biphenyl containing amino acids. Sugars are attached to the peptide unit resulting in compounds frequently in the molecular weight range of 1400–2000. These antibiotics inhibit bacterial cell-wall biosynthesis by binding to D-alanyl-D-alanine units found in the cell walls.

4.6. Lincomycin. The lincomycins and celesticetins are a small family of antibiotics that have carbohydrate-type structures. Clindamycin, a chemical modification of lincomycin, is clinically superior. Antibiotics in this family inhibit gram-positive aerobic and anaerobic bacteria by interfering with protein biosynthesis.

4.7. Lipopeptides. Polymyxin and daptomycin are examples of lipopeptide antibiotics that are used to treat bacteria infections in humans that are resistant to commonly used antibiotics. The structures of these two antibiotics contain a fatty acid side chain linked to different types of cyclic peptides. Polymyxin inhibits gram-negative bacteria and daptomycin inhibits gram-positive bacteria. Both antibiotics destroy bacteria by disrupting bacterial cell-wall membranes. Echinocandin and related lipopeptide antibiotics are very effective against fungal infections in humans. These antibiotics destroy fungi by inhibiting β-(1,3) glucan synthase, a critical fungal cell-wall component.

4.8. Macrolides. Antibiotics in the macrolide group are macrocyclic lactones that can be further classified into two main subgroups: (*1*) polyene macrolides that are antifungal agents and include compounds like nystatin and amphotericin B; and (*2*) antibacterial antibiotics represented by erythromycin, tylosin and azithromycin. The polyene antifungal antibiotics disrupt the fungal membranes to cause cell death. The antibacterial macrolides destroy bacteria by inhibiting protein synthesis. A number of other subfamilies of antibacterial and antifungal antibiotics fall into the broad category of macrolides.

4.9. Polyethers. Antibiotics within this family contain a number of cyclic ether and ketal units and have a carboxylic acid group. They form complexes with monovolent- and divalent cations that are soluble in nonpolar organic solvents. They interact with bacterial cell membranes and allow cations to pass through the membranes causing cell death. Because of this property they have been classified as ionophores. Monensin, lasalocid, and maduramicin are examples of polyethers that are used commercially as anticoccidial agents in poultry and as growth promotants in ruminants.

4.10. Tetracyclines. The tetracyclines are a small group of antibiotics characterized as containing a polyhydronaphthacene nucleus. Commercially, the tetracyclines are very important. They have been used clinically against gram-positive and -negative bacteria, spirochete, mycoplasmas, and rickettsiae and have veterinary applications in promoting growth and feed efficiency. The mode of action is inhibition of protein synthesis. Some of the more important members of this family are tetracycline, minocycline, and doxycycline.

4.11. Synthetic Antibacterial Agents. The fluoroquinolones have a significant portion of the antibacterial market; however, they are not defined as antibiotics since they were not derived from microbial products or based on structures of microbial products. The fluoroquinolones are synthetic antibacterial agents that are unrelated by structure to any natural product. They were discovered by screening synthetic compounds for antibacterial activity. Norfloxacin and ciprofloxacin are examples of these types of compounds and they have a significant market position in the control of bacterial infections in humans. These particular compounds inhibit growth of bacteria by inhibition of DNA gyrase, an enzyme involved in DNA replication. Another important family of synthetic antibacterial agents is the oxazolidinones. Linezolid is an important member of this structural family and it inhibits protein synthesis in bacteria by interfering with messenger RNA (mRNA) translation.

5. Discovery and Production

Most of the microorganisms used to produce antibiotics were isolated from soil samples and are categorized as actinomycetes. These types of microorganisms occur as heterogenous populations and generally inhabit the top few centimeters of soil. Families demonstrated to produce antibiotics include actinomycetes, bacteria, and fungi. Actinomycetes are the most productive for antibiotics. Until 1974, antibiotics produced by actinomycetes were almost exclusively from the genus *Streptomyces*, accounting for 95% of the total of ~2000 antibiotics known at that time. Thereafter, the role of "rare" actinomycetes as an antibiotic source became apparent as these latter organisms provided ~25% of the ~1100 antibiotics from actinomycete origin discovered in the next 6 years. The rare actinomycetes include organisms, eg, *Actinoplanes, Micromonospora*, and *Nocardia* species. Their capacity to produce diverse antibiotic structures is comparable to *Streptomyces*; however, the isolation of these organisms is less frequent by conventional isolation techniques (14).

To obtain reproducible antibiotic production by fermentation, it is necessary to obtain a pure culture of the producing organism. Pure cultures are isolated from mixed-soil sample populations by various streaking and isolation techniques on nutrient media. Once a pure culture has been found that produces a new antibiotic typically on a milligram per liter (mg/L) scale, improvement in antibiotic yield is accomplished by modification of the fermentation medium or strain selection and mutation of the producing organism. Production of gram per liter (g/L) quantities up to 30 g/L or more may take years to accomplish.

The vast majority of new antibiotics were discovered from screening soil microorganisms for production of antibiotics or by semisynthetic modification

of naturally occurring antibiotics. Screening soil microorganisms involved isolation of the organisms, fermentation of these isolates to produce microbial metabolites, selection of fermentations with antibiotics active against target bacteria or other organisms, and a dereplication scheme to eliminate known antibiotics.

Dereplication schemes sometimes involved mechanism of action screens to narrow the field of antibiotics detected and to select antibiotics with a mechanism of action unique to the target organism and perhaps less toxic to mammalian cells. One alternative approach, termed directed biosynthesis, involves feeding potential biosynthetic precursors into a fermentation of a known antibiotic in order to produce new components (14–16). This approach was used in the early development stages of the penicillins to obtain penicillin G. Phenylacetic acid was fed to fermentations of *Penicillium chrysogenum*. Another approach involves bioconversions. A known antibiotic is added to the fermentation of a microorganism that is capable of carrying out a process, eg, hydroxylation or amination. Modifications of these types can frequently be accomplished with a selectivity that is difficult to obtain by synthetic methods. A procedure called mutasynthesis, first reported with regard to new antibiotics related to neomycin (12,18), is sometimes used.

Genetic engineering technology has evolved that allows modifications of the microorganisms' DNA to produce new material. The structure of indolizomycin, the first new antibiotic obtained by a procedure known as protoplast fusion (19), was totally different from the antibiotics produced by the grandparental strains of *Streptomyces griseus* and *S. tenjimariensis* used in the fusion experiment. Cloning of genes involved in antibiotic biosynthesis from actinomycetes has become possible. The generation of the mederrhodin A producing *Streptomyces* clone was the first example of antibiotic production using *in vitro* recombinations (20). Gene segments from *S. coelicolor*, the producer of actinorhodin, were introduced into *Streptomyces* sp. AM7161, the producer of a related antibiotic called medermycin. Through this manipulation a clone producing a new medermycin derivative was obtained. Further extensions of these early gene manipulation studies including targeted gene disruption–replacement, heterologous expression, hybrid pathway construction, enzyme and pathway evolution, and combinations of all these techniques has been termed combinatorial biosynthesis (21). Numerous novel antibiotics and other polyketide metabolites have been produced by these methods. In genetic terms, low molecular weight antibiotics are quite complex. Gene clusters producing antibiotics commonly contain 10–50 genes to encode the synthesis of an antibiotic that has a molecular weight <1000. In contrast, a single gene can encode a very large protein. Within the antibiotic gene clusters are antibiotic biosynthesis genes, regulatory genes that regulate the gene clusters in which they are found, and antibiotic-resistant determinants (22).

Most of the new commercial antibiotics have resulted from semisynthetic studies. New cephalosporins, a number of which are synthesized by acylation of fermentation-derived 7-aminocephalosporanic acid, are an example. Two orally active cephalosporins called cefroxadine and cephalexin are produced by a synthetic ring-expansion of penicillin V. In the process of discovering these and other new semisynthetic β-lactams with commercial value, thousands of new compounds were synthesized and screened for antibacterial activity.

Commercial fermentations are conducted in large bioreactors that are usually referred to as fermentors and are designed for operation in batch, fed-batch, or continuous fermentation modes (23). The organism is grown at constant temperature in a sterile nutrient medium, containing a carbon source, a nitrogen source, and a small amount of inorganic salts, under controlled conditions of aeration and agitation. The media for commercial fermentations are usually complex mixtures containing relatively inexpensive nutrients, eg, molasses, corn steep liquor, or soy meal. A batch fermentation is a closed system containing sterilized medium inoculated with the desired microorganism. Incubation is allowed to proceed under optimal physiological conditions and nothing is added during the course of the fermentation except oxygen, an antifoam agent, and acid or base to control the pH. In the fed-batch process, nutrients are added in increments as the fermentation progresses. In the continuous fermentation, nutrient solution is added to the bioreactor continuously as an equivalent volume of converted nutrient solution with microorganisms is simultaneously removed from the system for processing.

The batch and fed–batch procedures are used for most commercial antibiotic fermentations. A typical batch fermentor may hold >150,000 L. When a maximum yield of antibiotic is obtained, the fermentation broth is processed by purification procedures tailored for the specific antibiotic being produced. Nonpolar antibiotics are usually purified by solvent extraction procedures; water-soluble compounds are commonly purified by ion-exchange methods. Chromatography procedures can readily provide high quality material, but for economic reasons chromatography steps are avoided if possible.

6. Economic Aspects

The world antibiotic market in 2006 was estimated to be near $30 billion/year. In 1996, the total world antibiotic market was estimated to be near $23 billion and the β-lactam antibiotics, particularly penicillins and cephalosporins, accounted for >65% of that market. In contrast, the total world sales for antifungal products was ∼ $3 billion at that time and the antiviral market was ∼ $2.6 billion. The distribution of sales of antibacterial antibiotics in the United States by structure class is given in Table 2 and this generally reflects the corresponding world market (24). In 1945 the production cost for a kilogram of penicillin was $11,000 and by 1995 this cost had dropped to $4.50 (25). This reduction in cost was a reflection of production going up and cost going down. The advance into a whole new technology that allowed this cost change to occur was termed strain improvement. By strain selections involving natural selections and mutation studies, the fermentation yields of the antibiotic derived from the improved strain were dramatically larger, which resulted in a corresponding price reduction in production costs.

Approximately 15 years ago most antibiotics were manufactured by major pharmaceutical firms. With a large number of antibiotics becoming generic and the profitability becoming significantly less, the manufacturing picture has changed. Europe remains the dominant manufacturing area for both penicillins and cephalosporins. However, more bulk manufacturing is moving to the Far East

with China, Korea, and India becoming major production countries. Dosage form filling is becoming more dominant in Puerto Rico and in Ireland (24).

Because of economic aspects, research to discover new antibiotics has shifted over the last several years from the large pharmaceutical companies to small and intermediate size companies. This change in part reflects the market size required by very large organizations in order to justify research in a particular area. Through mergers very large pharmaceutical companies have evolved and this has influenced the type of research they conduct. For example, the market for the anti-infective area is much smaller than the market for pharmaceuticals for cardiovascular and metabolic diseases. In many cases, the small and intermediate size companies conducting research on the discovery of novel anti-infective agents are usually dedicated to one area of infectious diseases or one area in the discovery process.

Japan held 37.5% of the world antibiotic market in 1988, the United States 23.2%, Italy 8.0%, the United Kingdom 5.4%, Germany 3.6%, and other countries 22.3% (26). The disproportionate size of the Japanese market was in part a consequence of the inherent strengths of Japanese industry that included expertise in fermentation technology and intensive chemical manipulation of known structures. In addition, antibiotic prescribing in Japan was extremely popular among doctors as a result of the Japanese reimbursement system.

7. Uses

7.1. Antibacterial Agents. There is a continuous need for new antibiotics primarily as a result of bacterial resistance. There are two aspects to this phenomenon. First, as the more common pathogens are controlled by antibiotics, less common, highly resistant organisms present more prominent health problems. Examples are infections resulting from *Pseudomonas* and *Enterobacter*. Second, and this has been the major driving force in the antibiotic market, particularly in the hospital sector, there is emerging resistance (see the section Development of Resistance). This type of bacterial resistance can take place through one or more mechanisms including reduced target affinity, target bypass, drug inactivation, reduced permeability of bacterial cells, and drug efflux from the organism. Resistance can be passed from one organism to another through plasmids that are highly mobile segments of bacterial DNA. This transfer of resistance can even occur between different species and genera of bacteria.

The development of new antibiotics to combat resistance, and to provide easier oral administration and improved pharmacokinetics, has been successful through synthetic modifications. This approach has been particularly rewarding in the area of β-lactams. The commercial importance of the β-lactams is evident from the market share of antibacterials (Table 2). Fully 65% of the 2003 world antibacterial market belonged to the cephalosporin and penicillin β-lactams (24).

7.2. Anticancer Agents. In the latter 1980s, antibiotics became more important in the treatment of cancer. By 1987, the antitumor antibiotic adriamycin [23214-92-84] was one of the top 50 drugs worldwide. Other important antibiotics clinically used for treatment of cancer include bleomycin [11056-06-7] and mitomycin C [50-07-7]. These compounds are all toxic both to bacteria and to

mammalian cells because they interact with DNA. Although antibiotics of this type are not useful as antibacterial agents because of their toxicity and resulting low safety margins, they are useful as antitumor agents. They do show some selective toxicity to rapidly proliferating cancer cells. One of the recent approaches to new anticancer agents has been the conjugation of an antitumor antibiotic to a monoclonal antibody to obtain an antitumor agent that is selectively targeted to a particular tumor type. This approach reduces toxic effects of the antibiotic by utilizing the selective targeting of the monoclonal antibody to cancer cells. Calicheamicin is an extremely potent antitumor antibiotic with a very unique chemical structure that was linked to a monoclonal antibody to obtain an anticancer agent called Mylotarg. This product proved successful in clinical trials and was introduced onto the pharmaceutical market in the year 2000. Mylotarg was the first antibody-targeted chemotherapeutic agent registered for humans (27).

7.3. Antituberculin Agents. Rifampin [13292-46-1], a semisynthetic derivative of rifamycin SV, is a most valuable drug for treatment of tuberculosis, leprosy, and an expanding range of other infections caused by mycobacteria (28). Cycloserine [64-41-7] and streptomycin [57-92-1] have been used to a limited extent for treatment of tuberculosis as a reserve antibiotics. Although cycloserine inhibits bacteria by interfering with their cell-wall biosynthesis, it has toxic side effects in humans in the form of neurotoxicity. Capreomycin [11003-38-6] and to a much lesser extent viomycin [32988-50-4], both of which are peptides, have also been used for treatment of this disease.

7.4. Antifungal Agents. Antibiotics have been effective in the treatment of fungal diseases. Because these types of infections are less prevalent than bacterial infections in the United States and Europe, the market for antifungal antibiotics has been relatively small. Candidemia is the most deadly of the common hospital-acquired bloodstream infections with a mortality rate of $\sim$40% (29). In the United States there are an estimated 60,000 cases per year. As the number of immunocompromised patients increases as a result of therapy following organ transplants, acquired immunodeficiency syndrome (AIDS), and anticancer chemotherapy, the need for new and improved antifungal agents may increase significantly. Amphotericin B [1397-89-3], a polyene antibiotic, remains a useful drug for systemic treatment of serious fungal infections despite its inherent toxicity (30). More recently, amphotericin B has been formulated as a liposomal preparation in an effort to reduce toxicity. Other clinically used antifungal polyene antibiotics include nystatin and pimaricin [7681-93-8], however, applications are essentially limited to superficial infections. They are too toxic for parenteral administration. One of the most recent antifungal antibiotics approved for systemic use including candidemia in humans is anidulafungin, a semisynthetic lipopeptide of the echinocandin family (29). Griseofulvin [126-07-8], which has a structure containing a spiro ring system, is a very good antibiotic for treatment of dermatophyte or ringworm infections.

7.5. Antiviral Agents. Although a number of antibiotics have been shown to have some sort of antiviral activity, only vidarabine [5536-17-4] (adenine arabinoside) is used clinically against viral infections at this time. Vidarabine has been produced by fermenting a strain of *Streptomyces antibioticus*, but it originally was discovered screening synthetic compounds. Many of the

previous uses of vidarabine have been superseded by acylclovir, an antiviral agent with improved biological properties that is a synthetic product. As the need for new antiviral agents increases and new screening procedures are developed, one would expect the discovery of other new effective antiviral antibiotics that could be used safely in human therapy.

7.6. Veterinary Applications. Another use for antibiotics is for veterinary applications and for animal feed supplements to promote growth in livestock. Feed antibiotics used in the United States far surpass all other agricultural applications in terms of kilogram quantities used and approach quantities used in human medicines (30). The extensive use of antibiotics in feed additives has over the years raised concerns about the development of antibiotic resistant bacteria (31).

The feed additive antibiotics market is dominated by tetracyclines and tylosin [1401-69-0] (32). Other important feed antibiotics include bacitracin, virginiamycin [11006-76-1], bambermycin [11015-37-5], lincomycin, and spiramycin [8025-81-8]. The growth promoting effect of most of these antibiotics is believed to result from subtherapeutic treatment of diseases. In addition, there is another group of antibiotics that effect growth rate and feed efficiency in livestock in the absence of disease. Key products in this area include the polyether ionophores monensin [17090-79-8] and lasalocid [25999-31-9] and the glycopeptide avoparcin [37332-99-3].

Coccidiosis is a protozoal disease of the intestinal tract of animals that leads to severe loss of productivity and death. The development and widespread use of anticoccidials has revolutionized the poultry industry. The market for anticoccidial agents is dominated by the polyether ionophore antibiotics monensin, salinomycin [53003-10-4], narasin [55134-13-9], lasalocid, and maduramicin [84878-61-5] (32).

Antimicrobials, a diverse group of products including antibiotics for therapeutic treatment, represent the largest sector in the animal pharmaceutical area. The tetracycline antibiotics represent the largest part of this group. Penicillins and macrolides also represent large segments of this market (32).

Another very important agricultural application for antibiotics is in the area of anthelmintics. The most significant single anthelmintic agent is ivermectin [30288-86-7] (32).

Ivermectin is the catalytic reduction product of avermectin, a macrolide containing a spiroketal ring system. Two other related antibiotics having significantly different structural features and biological properties, moxidectin and milbemycin oxime, were more recently introduced into the market. Although these compounds have no antimicrobial activity, they are sometimes referred to as antibiotics because they are derived from fermentation products and have very selective toxicities. They have potent activity against worms or helminths and certain ectoparasites, eg, mites and ticks.

8. Development of Resistance

The development of resistance in *Staphylococcus aureus* and other microoganisms to antibiotics can be considered a process of evolution. The prolonged

exposure of bacteria, fungi, and other microorganisms to antibiotics in a hospital and nursing home environments over a period of time results in a selection process in which certain organisms in a very large population survive since they have enzymes or other processes to deactivate the antibiotic. These surviving organisms multiply to form colonies of the resistant organisms that can cause infections. An example of these types of organisms is methicillin resistant *S. aureus* (MRSA). These resistant bacteria appear to be less capable of competing with antibiotic sensitive bacteria in a natural environment since they carry additional DNA to counter act the antibiotics thus requiring greater energy demands. The resistant organisms survive well in a hospital environment were populations of antibiotic sensitive organisms have been greatly reduced and offer no significant competition. However, in a natural or wild environment they are at a disadvantage to the wild-type organisms that dominate (31). More recently, some antibiotic resistant bacteria have caused infections outside the hospital environment that has created great concern.

A brief review of the development and treatment of MRSA infections gives a better insight into this emerging resistance problem. The penicillins were some of the first and definitely the most useful antibiotics for treating bacterial infections in humans. Within a few years after the first clinical use of penicillin in the 1940s, resistance was detected due to inactivation of penicillin by β-lactamases that had developed in *S. aureus*. Methicillin, a semisynthetic penicillin that was stable to β-lactamases, was introduced into the market in 1959. Within a year, MRSA strains were identified. The introduction of vancomycin onto the market for human therapy against gram-positive bacteria occurred near 1959. Vancomycin represented a new structure class for clinically used antibiotics, but was used only in limited amounts until ∼1980 when MRSA became a significant problem in hospital environments. Vancomycin was very effective against these infections and by 1990 it had become one of the most effective antibiotics used in hospitals against MSRA. However, by 1997 resistance to vancomycin was becoming a significant problem, not only for MRSA strains with reduced susceptibility to vancomycin, but also for vancomycin-resistant enterococci (VRE). As a result, new antibiotics were introduced for use against these vancomycin-resistant bacteria. One of these was daptomycin, which was discovered in 1988, but found to have no advantages for use in humans at that time. Later, when the resistance problems with vancomycin became a serious problem, daptomycin was reinvestigated and found very active against these vancomycin-resistant strains. Daptomycin was introduced onto the market in 2003 and represents a new structure class for antibiotics that are used in humans. A new antibiotic structure class usually results in an antibiotic that is effective against the existing antibiotic resistant organisms since these organisms have not been exposed to the new type of structure and its corresponding unique mechanism of action.

Similar problems have evolved with the development of resistance in gram-negative bacteria against antibiotics, eg, the aminoglycosides, β-lactams, and the quinolones.

With fungal infections, the broad spectrum antifungal antibiotic amphotericin B has remained an important agent to combat serious fungal infections resistant to other antifungal antibiotics. However, it has serious toxic effects in

humans and its use has been limited, which may explain in part the very slow development of resistance to amphotericin B.

The development of resistance in bacteria and other microorganism to antibiotics used in treating infectious diseases remains a very serious problem. However, the continuing introduction of new antibiotics that are effective against the resistant organisms, the efficient use-management of currently available antibiotics, and new research strategies against antibiotic resistance should provide effective approaches to combating this problem.

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Table 1. **Year of Discovery or Market Introduction of Some of the More Important Antibiotics for Human Use**

Antibiotic	CAS Registry Number	Year	
		Discovery	Introduction
Penicillin		1929	1940
Tyrothricin	[1404-88-2]	1939	
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Griseofulvin	[1403-70-9]	1939	
Streptomycin	[57-92-1]	1944	
Bacitracin	[1405-87-4]	1945	
Chloramphenicol	[56-75-7]		1947
Polymyxin	[1406-11-7]	1948	
Chlortetracycline	[57-62-5]		1948
Cephalosporin C	[61-24-5]	1948	
Neomycin	[1404-04-2]	1949	
Oxytetracycline	[79-57-2]		1950
Nystatin	[1400-61-9]	1950	
Erythromycin	[114-07-8]		1952
Novobiocin	[303-81-1]	1955	
Vancomycin	[1404-90-6]	1955	1959
Amphotericin B	[1397-89-3]	1955	
Kanamycin	[8063-07-8]		1957
Ampicillin[a]	[69-53-4]		1962
Fusidic acid	[6990-06-3]		1961
Cephalothin[a]	[153-61-7]	1962	
Lincomycin	[154-21-2]		1963
Gentamicin	[1403-66-3]		1963
Carbenicillin[a]	[4697-36-3]	1964	
Cephalexin[a]	[15686-71-2]	1966	
Clindamycin[a]	[18323-44-9]		1967
Cephaloxidine and cephalothin[a,b]			1969
Minocycline[a]	[10188-90-8]		1971
Amoxycillin[a]	[26787-78-0]		1972
Cefoxitin[a,c]	[35607-66-0]		1978
Tricarcillin[a]	[34787-01-4]		1979
Mezlocillin[a]	[51481-65-3]		1980
Piperacillin[a]	[61477-96-1]		1980
Cefotaxime[a]	[63527-52-6]		1980
Moxalactam[a]	[64952-97-2]		1981
Azithromycin	[83905-01-5]	1982	
Augmentin[d]	[74469-00-4]		1984
Aztreonam[e]	[78110-38-0]		1984
Imipenem[a,f]	[74431-23-5]		1985

Table 1. (*Continued*)

Antibiotic	CAS Registry Number	Year	
		Discovery	Introduction
Daptomycin[a]		1988	2003
Anidulafungin[a]			2006

[a]Semisynthetic products.
[b]First oral cephalosporins.
[c]First commercial cephamycin.
[d]First β-lactamase inhibitor combination.
[e]First monobactam and a synthetic product.
[f]First carbapenem.

Table 2. **1999 United States Antibiotic and Antibacterial Agents Market**[a]

Structural classification	Market share %
Cephalosporins	45
Penicillins	15
Fluoroquinolones (synthetic)	11
Macrolides	5
Tetracyclines	6
others	18

[a]1999 United States market estimated at $>\$8 \times 10^9$ (22).