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The Influence of Antimicrobial use on Bacterial Resistance

James T. Griffith
Walden University

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THE INFLUENCE OF ANTIMICROBIAL USE ON BACTERIAL RESISTANCE

JAMES T. GRIFFITH

DR. FRED ROLAND 6/22/92
Faculty Advisor DATE

DR. JAMES P. DIXON 7/24/92
Member, Review Com. DATE

DR. JOHN E. CANTELON
Vice President, Academic Affairs DATE

DR. JACOB GREEN 7/10/92
Member, Review Com. DATE

DR. GLENDON F. DRAKE
President, Walden University DATE

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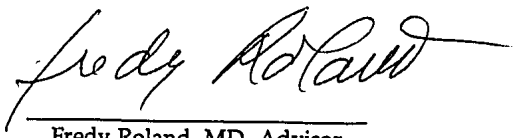
ABSTRACT

by

James T. Griffith

BS, University of Massachusetts Dartmouth, 1970
MS, University of Massachusetts Dartmouth, 1976



Fredy Roland, MD, Advisor
Professor of Microbiology
Brown University
Providence, Rhode Island

Dissertation Abstract Submitted in Partial Fulfillment of
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Abstract

Antimicrobial resistance is becoming an increasingly serious problem accompanied by relatively few studies examining the relationship between use and resistance. The present study undertakes a twenty year analysis of antimicrobial production and factors affecting antimicrobial use for a particular microorganism (Stp. faecalis)/antimicrobial agent (Cephalothin) combination. The period is inclusive of the market introduction of the agent and considerate of prescribing practices to the present time. The accumulated data reveal that there is indeed a relationship between total drug availability (medicinal, agricultural) and increased antimicrobial resistance. The data also suggest that national (or global) use changes would likely have a long term beneficial effect on the deteriorating circumstances surrounding microbial resistance to antimicrobial chemotherapeutic agents The methodology utilized includes analysis of primary historical data and graphical representation of indices derived from these data. A literature review examines the impact on antimicrobial resistance by historical duration of use, various mechanisms of resistance, non-medical uses of antimicrobial agents and clinical misuse.

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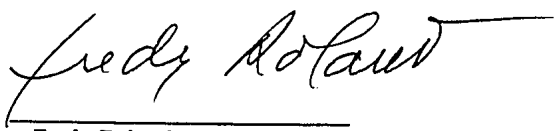

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Chapter I

Introduction

A report issued by the Great Britain Army Medical Directorate in 1945, evaluating the experience of Twenty-One Army Group with the first wide-ranging use of penicillin in history, stated:

> . . . it is fair to say that never before has penicillin been used either in prophylaxis or therapy on such a wide scale . . .. One would like to emphasize the prophylactic side of the picture.[1]

Almost thirty years later, the U.S. Deputy Assistant Secretary for Health said in an editorial addressed to the medical community, "the prophylactic use of antibiotics should undergo the greatest scrutiny, since this common use (especially in surgery) is supported by very few appropriately designed . . . trials . . .." [2] This view had been spoken before [3] and increasingly since.[4,5,6]

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The significance in this turnaround lies in the alarming increase of microbial resistance [7,8] to the many antimicrobial agents now in use. At the International Symposium of New Trends in Antibiotics (Milan, Italy, 1980) Bernd Wiedmann commented, "like a shadow the emergence of antibiotic resistant bacteria followed the introduction of every new antimicrobial drug." Whether this situation is due to use is not entirely clear, but at a hearing in Washington, D.C. on December 7, 1982 on the misuse of antibiotics, Senator Gaylord Nelson of the Subcommittee on Monopoly of the Select Committee on Small Business stated that antibiotics are among the most frequently prescribed drugs in this country, exceeded only by the psychoactive drugs. Calvin M. Kunin concluded that "antibiotics are overused in this country." [9]

Problem

Antimicrobial resistance is becoming an increasingly serious problem in the treatment of many types of infectious disease. Although the fact of increased resistance is widely known, few [10,11,12] studies have examined the relationship between use and resistance. Further, the increase of this problem may have accelerated some time ago and the rate of magnitude may also be accelerating faster than originally thought.

Background

The statement by Alexander Fleming in 1929, commenting on his recent discovery of penicillin "It may be an efficient antiseptic for application to or injection into areas infected with penicillin-sensitive microbes" issued all of us into the much-celebrated antibiotic era. The cause for celebration was and is the tremendous decrease in mortality resulting from a large group of microorganisms. During the second World War, the western allies considered the production of these antimicrobial agents a major war effort. Their effect on the most dangerous and common infections resulting from war wounds clearly justified the intent. [13]

Since that time, however, serious problems have intervened. Selman Waksman was one of the first to reflect on these now serious difficulties in his early book on streptomycin. [14] After revealing that the organism responsible for the production of streptomycin was discovered at Rutgers University in September of 1943, he indicates surprise that before 1947, "the first observations were then made of the development of bacterial resistance to the drug . . .." A rather substantial medical/scientific literature has accumulated over the intervening one-third century, indicating that this trend has continued unabated and possibly encouraged by our subsequent

actions. In 1977, Faine [15] concluded that the resistance factors, by then well known among health scientists, were in fact "ubiquitous" throughout the world but were more common where the selection pressure of use increased frequency. If the current use rate is sustained, it may well spell an end to the antibiotic era and return us to a quality of life that few now remember and none would welcome. If the pressures leading to this conclusion are examined, they may illuminate a path to stem this eventuality.

Purpose

The purpose of this study is to compare the relationship between antimicrobial resistance levels and usage patterns of the antimicrobial(s) indexed. Selected for study was the cephalosporin, Cephalothin, and the resistance developed to it by *Streptococcus faecalis*. This microorganism/antimicrobial agent combination offers:

* Microorganism taxonomy and nomenclature stability adequate to the longevity of such a study.
* Prescribing practice stability regarding the offending organism in clinical situations and a single drug over a long period of time.

* Use of the same family of drugs in the general field of medicinal chemicals over the same period of study .

Thus, the fortuitous relationship between this microorganism/ antimicrobial agent and the long view of the study provide a platform for better understanding of the long-term effects of antimicrobial use. This understanding illuminates the course for societal change needed to deal with the emerging problem of widespread antimicrobial resistance.

Significance

Clearly, antimicrobial resistance to the now commonly used chemotherapeutics has received wide attention in recent years (Alfor, [16] Benveniste, [17] Cohen, [18] Finland, [19] Finland, [20] Godfrey, [21] Locksley, [22] Neu [23] and Wiedmann [24]). Many possible contributing factors have been suggested (Abramowitz [25], DiPiro, [26] Durbin, [27] Scheife [28] and Washington [29]); costs have been studied by hospital administrators, usage rates by hospital pharmacists, prescribing patterns by physicians' groups, but one factor that has received less attention than perhaps it deserves is the relationship between the amount of drug present in the environment (partly measured by

therapeutic consumption), and an organism's net response (bacterial population) to it over time. By examining the dynamic between these two, solutions to this situation of increased antimicrobial resistance may be suggested. Particular points in our use history may illuminate one of the above contributing factors over others as having more than its share of contributory weight. For example, the release date of a drug or the emergence of a new biological competitor may be thought important. A study of the use of previously restricted antibiotics in Czechoslovakia [9] suggests that availability/introduction encourages use beyond medical necessity. Indeed the observation that previously underutilized or unavailable tools in the treatment of infectious diseases often have initial short-term success, suggests that just such a longitudinal study as this may be the only way to see the problem as it is.

Methodology (Nature of the Study)

The study has used methodology of developmental research. The resistance levels of *Streptococcus faecalis* to a selected cephalosporin (Cephalothin) has been indexed at several points over a twenty-five (25) year continuum. This data is compared to the amount of cephalosporin available in the environment (production sales, prescriptions issued, etc.) indexed at comparable points.

Chapter II

Literature Review

A review of the literature reveals that antimicrobial resistance among microorganisms is a wide-ranging problem of long duration (hence the length of the study). Early chemotherapeutic agents available in the antibiotic era were commonly used in a prophylactic mode as has been pointed out earlier. Part of the situation this study has addressed stems from misinterpretations and/or unreasonable extrapolations of early protocols. For example, the British 21 Army Group's Manual on the Use of Penicillin (1945) makes it clear that:

> All the dangerous pathogens commonly found in war wounds are penicillin sensitive, and if one can get the penicillin into contact with them and maintain it there in an adequate concentration for a sufficient period of time these organisms should be inhibited or destroyed. [31]

Unfortunately, carrying this idea to general situations in the civilian population may tend to cause overuse. The probable success (in a Darwinian sense) of resistance plasmids [32,33] as opposed to

chromosomal [34] mutation resistance (once thought to be the only mechanism), can be suggested by the occurrence of antibiotic resistant organisms in unlikely settings, such as drinking water, [35] "non-pathogenic" organisms causing nosocomial infections, and various veterinary agricultural situations. [36] In fact, at the Congress on Antibiotics (Prague, 1964), Dr. A. Ch. Sarkisov of the All-Union Experimental Veterinary Institute, Moscow, U.S.S.R. suggested,

> "The problem of non-medical use of antibiotics was contained in two general directions. 1) the use of antibiotics by living bodies in the period of their varied vital processes. To this group belongs the application of antibiotics to cattle breeding, vegetable production and industrial microbiology. 2) the addition of antibiotics to food and other products of animal, vegetable and microbial origin." [37]

Many of these uses by this account and others involve massive environmental introduction of chemotherapeutics, either as multiple agent cocktails, or broad distribution to organisms diseased or not, or both. This may not be as direct a contributing factor of resistance as clinical misuse, but its promiscuity, in terms of not being directed at

specific cases, one at a time, may still be quite significant. This isn't to say that the case for clinical misuse cannot be made. For example, in a summary statement of data from other papers dealing with the reasons for misuse of antibiotics, Smith et al [39] suggests that a majority of patients receiving antibiotics have no evidence of infection, and up to half had no culture taken. The suggestion is also made that the "excessive use of antibiotics has led to the emergence of Gram-negative organisms which are resistant to multiple antibiotics." Other data [39] indicate that not only do organisms have measurable resistance patterns, but over time they can be seen to change. This study offers a method for long term documentation of such change.

Scope and Duration of the Problem

On the first of these points relating to the size of the problem, the literature is quite productive. A milepost in judging the scope of the problem may be forged by assuming that the date of insult relating to human stimulation of antimicrobial resistance is coincident with the dawning of the "antimicrobial era" and its rapid development and expansion during and after World War II. This indeed seems to be the case in concluding from the work of Hughes and Datta [40] that while plasmids were quite prevalent during the first part of the 20th

century, they were apparently not about the business of transferring antimicrobial resistance genetic information. This conclusion was made possible by evaluating the genetic status of organisms meticulously collected by the Canadian microbiologist, E. D. G. Murray from 1917 to 1954. Thus in the amount of time available, for we humans to have stimulated the huge genetic commitment on the part of microorganisms that we seemingly have, we have produced quite a sobering result. Clear antimicrobial resistance difficulties affecting human medical care now exist in such diverse economic, political and scientific environments as Germany, [41] Scotland, [42,43] Israel, [44] Norway, [45] Italy, [46] Thailand, [47] France,[48] Philippines,[49] Spain, [50] Nepal,[51] Sri Lanka, [52] Rumania, [53] New Guinea, [54] the United States, [55] and practically every other nation in the world where investigations have been done, according to a study [56] sponsored by the Fogarty International Center of the U. S. National Institutes of Health conducted from 1983 to 1986. The universality of this problem has been further documented in a set of sequential evaluations [57,58,59,60] reported on by the World Health Organization spanning a decade (1973-1982). This series of observations, common to many studies of lesser duration conducted during the 1950's through the 1970's, has the startling revelation that during the 1950's (the second decade of the "antibiotic era"), hospitals were the focus of antibiotic

resistance. This observed resistance was almost always to a single antimicrobial agent, first seen in *Staphylococcus aureus*, then later in various Gram-negative aerobic bacilli. By the early 1960's, the focus had shifted to include multiple drug resistance and being commonly isolated from hospitalized and non-hospitalized patients. In the latter part of the 1970's it had become apparent that at least some resistance to antimicrobial agents that an organism might possess may well be derived from widely different organisms and specifically organisms different from itself. [61] The literature is rich in its appreciation for the wide-ranging aspect of this problem and generally does not dispute the experience and findings of the international microbiology community. [62,63,64,65,66,67] The resultant literature provided some early clues for the duration of the antimicrobial resistance problem:

> Paul Ehrlich in 1907 described the trypanocidal activity of *p*-rosaniline, and in the same year his research group reported that *Trypanosoma brucei* became resistant by repeated exposure to the drug. Knowledge of drug resistance in microorganisms is therefore as old as the history of chemotherapy itself. Drug resistance of bacteria was reported by

Morgenroth and Kaufmann (1982) soon after discovery of the anti - pneumococcal effect of ethyldihydrocupreinehydrochloride (optochin). [68]

We have come to expect this response of resistance to our chemotherapeutic agents on microorganisms not in months or years but rather during the treatment of a single episode in our patients. [69] In the retrospection that the literature provides, this response has also been appreciated almost from the beginning of the anti-microbial era in the treatment of war wounds, [70] hospital infections, [71] and typhoid fever. [72]

Mechanisms of Resistance

In a well known series of studies by Finland et al. [73,74,75] the established fact of antimicrobial resistance variability exhibited by streptococci was shown to be increasingly manifest in its diversity regarding different antibiotics, as demonstrated within strains of the same or related species. Further as one of the very early appearances of this idea in the literature, one of the chief conclusions of these studies related to the description of a distinctive pattern of sensitivity. The commonly held feeling at that time was that antimicrobial resistant strains were the result of the "elimination of naturally sensitive strains" and

subsequently the "persistence and spread of naturally resistant strains of the same species." The literature further reveals that Finland recognized that quick emergence of resistant strains occurs during the treatment of some patients. [76] Also evident in the literature of this time was that unexpectedly resistant strains of some organisms complicate certain cases. [77] These observations occur elsewhere in the literature of the time. [78,79,80,81,82,83,84]

Explanations for observations of the fundamental differences between sensitive and resistant strains of bacteria did appear. Klimer, et al[85] suggested that resistant organisms may grow more slowly, while others [86,87,88,89] proposed various metabolic pathway alternatives to explain the phenomenon. Anderson [90] suggested "a number of metabolic and biochemical changes found in a patient isolate of *Staphylococcus spp.* correlated with resistance to five antibiotics." Phases of the bacterial cell cycle were also examined for possible contributions to resistance [91]. The concepts of bacterial persistence, [92,93] virulence [94] and cross resistance [95,96,97,98] were developed from these investigations. Theories and proposals have continued through to the present time regarding groups of micro- organisms [99,100,101,102] in varying circumstances [103,104,105,106].

Further evidence as to the persistence of this problem began to appear in the literature of the 1970's and included the evidence of various international comparisons. [107,108] A major conclusion was that not only is there variable resistance but that there may be local human practices that enhance it. [109,110,111,112] The innovative contribution of this decade was the comparison and analysis of these data by computer methods. [113,114]

By the ninth decade of the century the focus had shifted to the ways in which various *status quo* resistance patterns changed over time [115,116]. This view eventually brought us to the present mechanistic considerations involving microbial alteration of antibiotic receptors [117,118,119] decreased entry of anti-microbial agents, [120,121,122] and destruction or inactivation of antimicrobial agents. [123,124]

Eventually antimicrobial resistance was described in evasive terms reminiscent of post transplantation definition of "life." [125] This description is due in part to the previously mentioned casual reckoning of antibiotic prophylaxis. [126,127] As has been suggested from conclusions of the landmark study by Datta on the pre-

antimicrobial agent era cultures of E.D.G. Murray, above mentioned, the literature does allow that while antimicrobial resistance probably predated the widespread scientific use of purified antibiotics, [128] it was probably of low frequency [129] since the challenge that would have made expressing and carrying the extra genetic information beneficial in the Darwinian sense was low. [130,131] Misinterpretations [132] and unreasonable extrapolation [133] of early success have led in part to our current predicament. The literature provides many well-documented examples. For example, a three-month study conducted at a 370-bed university-affiliated VA hospital revealed that empiric prescribing patterns for suspected infectious disease situations were wrong 28% of the time when decisions were made prior to culture and sensitivity reports being available, and that prescribing on the basis of "past clinical experience" with an agent were wrong 71% of the time.

The authors of this study concluded that attempts to influence prescribing should be directed at "changing the prescribers' response to the stimuli to prescribe and beliefs regarding the perceived outcome of drug therapy." [134] In another example, a rather daring study by Price and Sleigh[135] showed that the

infection rate of multi - drug resistant strains of *Klebsiella spp.* in a neuro-surgical unit was reduced from 50% to 15% only after the cessation of all antimicrobial use. Various statistical methods have been developed [136] to predict and potentiate patient outcomes from situations relating to infections with resistant vs. non-resistant microorganisms, but in major studies such as Holmberg's review [137] of 175 published and unpublished reports:

> . . . The likelihood of hospitalization, and the length of hospital stay were usually at least twice as great for patients infected with drug-resistant strains as for those infected with drug-susceptible strains of the same bacteria.

Role of Plasmids in Resistance

On the matter of the fourth point of this literature review, it is clear that a significant amount of our current difficulty stems from the effects of shared plasmids that transmit information from one microorganism to another relative to the various processes of antimicrobial resistance. [138] These plasmids were conceived of early on in work appearing in the eighth decade of this century as consisting of:

> . . . two major segments: a segment responsible for the expression of drug resistance, and a segment capable of conferring the ability of episomic autonomy such as replication and sexual transfer. [139]

Since then various methods of transfer have been proposed, [140] and plasmid transfer maps [141] have been used to allow better understanding of the relationship between many closely related microorganisms.

That resistance plasmids are central to the size of the problem in antimicrobial resistance today is scarcely debated and is generally accepted the world over. [142] More to the point of this present investigation is the examination of how these plasmids come to be [143] and what factors drive their persistence. [144] In the period attending the discovery and introduction of the earliest chemotherapeutically active antimicrobial agents, resistance was observed in short order as has been reviewed in this chapter. The earliest assumptions used in attempts to explain this resistance centered around chromosomal mutation scenarios. [145] Indeed, there are examples [146,147] of this in nature. It is, however, the extra chromosomal encoding of resistance that has gained greatest attention in the decades of the most intense

and productive investigation. [148,149] The very transmissibility of these genetic agents soon became the focus of researchers [150] the world over and has been expanded and clarified to distinguish between plasmids, episomes and transposons. [151] By the early 1980's so much was known about extra-chromosomal elements and their participation in the antimicrobial process that mechanisms of purging them from the corpus of a bacterium or "curing" were being investigated and tested.[152] Nonetheless, microorganisms containing and indeed sharing these elements have been chronicled in the literature as taking an increasing toll on the morbidity and mortality of infectious disease patients, [153] and efforts to define the source [154] and the method of spread were underway by the mid 1970's. [155] The ubiquity of discovery from the subsequent literature suggests that perhaps a combination of agents may be necessary to affect the desired outcome in the next phase of our relationship with the disease producing microorganisms. [156] The nature of the role of human practice at inducing the frequency of drug resistance plasmids [157] is an especially chilling contemplation. The enterococci appear to have been especially respondent [158] to this stimulus and indeed are the focus of the present study.

The relatedness of plasmids and how they are shared by inter- and intra-species events has also been described in the literature. [159] Palomares and Perea showed, for example, that "the frequency of transferable drug resistance among resistant *Salmonella* was 75%" and that as much as 94% of all resistant strains of *E. coli* carried resistance plasmids. [160] The works of Jorgensen and Johnston and Kolator further demonstrate that this relatedness shows itself again in that "Animals and human beings who share an environment exchange microorganisms. [161] The Jorgensen work describes very closely related *E. coli* plasmids in piglets and humans in Denmark, [162] while the Johnston and Kolator paper describes a 3.2 megadalton ß-lactamase "African-type" encoding plasmid of *Neisseria gonorrhoeae* found in the Netherlands, Canada and the U.K. [163] At this point the issue of transferability becomes significant in our appreciation of the impact of extra-chromosomal resistance in modern medicine. [164, 165] Throughout the 1980's various examinations of conjugation and other modalities appear in the literature. [166] A paper by Mays [167] in 1982 was characteristic of several others [168, 169, 170] in the late 1970's and early 1980's describing novel antibiotic resistance transfer that leads directly to the contemporary situation. Malamy and Tally [171] were among many by the end of the decade who had described gene transfer of antimicrobial resistance factors between unrelated

species. The literature of the previous decade also had a thorough review and debate over the issues of multiresistant microorganisms[172] and the global forces that encouraged this now quite common phenomenon in the world's health care facilities. The combined problems of multiple drug resistance [173] and self transferability abundantly demonstrated in the literature influenced Lowbury and Ayliffe [174] to first propose that "we may see the decline of useful antibiotic therapy in 40 years." This avenue of the literature leads in part to the current study. Moellering [175] has suggested recently that the ß-lactamase resistance genes of enterococci are a product of this transferability function of plasmids through evidence of their staphylococcal origin. Earlier studies have corroborated important parts of this dilemma relating to a staphylococcal resistance mechanisms [176] and the exogenous acquisition by enterococci of resistance plasmids. [177]

Effect of Non-medical Uses of Antimicrobial Agents on Resistance

The stimulatory effect on plasmids, episomes and transposons coding for antimicrobial resistance is not limited to human-medicine related activities. The abuses (from an antimicrobial resistance standpoint) of the many non-medical uses of antimicrobial agents have appeared

in the literature since the 1950's. [178] In a sweeping review in 1987, DuPont and Steele observe that:

> Nearly half of the antimicrobial agents now sold in the United States are used either therapeutically or sub-therapeutically in animals. A considerable portion of these drugs are ionophores that are not used as therapeutic agents in humans or animals. The majority of the non-pet animals that are so treated end up in the food chain for human consumption. Antimicrobial agents are given to animals in subtherapeutic concentrations for three reasons: (1) to prevent infectious diseases caused by bacteria or protozoa; (2) to decrease the amount of feed needed; and (3) to increase the rate of weight gain. It is generally appreciated that the use of subtherapeutic levels of antimicrobial agents is one tool that has facilitated confinement housing, allowing larger numbers of animals to be maintained in production facilities of a given size. This practice apparently has contributed to lower

> costs of animal care and ultimately to a lower cost to the consumer for meat, milk and eggs. [179]

This basically states the experience of the western world since World War II. This million or so kilograms of antimicrobial agent use [180] is distributed such that 80% of poultry, 45% of swine, 60% of feedlot cattle and 75% of dairy calves marketed or raised in the U.S. are estimated to have been fed an antimicrobial agent at some time during life. [181] The subtherapeutic levels of antibiotics employed in feeds for growth-promoting purposes in the U.S. range from 2g to 200g/ton of feed (2.2-220 ppm). For the prophylaxis of infection among so-called stressed animals (i.e., those undergoing shipping, weaning, or abrupt environmental change), the concentration is increased to 100-400 g/ton (110-440 ppm); the increased dose is given to chickens for three to five days and to livestock for two to three weeks. For the treatment of active infection, these drugs are given in a still-higher dose; 200-1,000 g/ton (220-1,100 ppm). For therapy, additional drugs may be added to water or injected parenterally.

Despite regulation of these substances via the Kefauver-Harris Amendment of the Food, Drug and Cosmetic Act of 1938 and the establishment of the National Research Council to study the Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds in the U.S., the joint Agricultural and Medical Research Council Committee in the U.K. and similar efforts in other countries, resistance generated in enteric organisms from chickens, pigs, sheep and cattle fed antibiotics for growth enhancement, and the spread of such bacterial resistance to regional farm workers persist. [182] Along with this, the continual flow of detectable levels of antimicrobial agents continues into the human food chain. [183,184,185,186]

By the mid 1980's, the whole relationship between human and animal physiology in these matters had become so blurred that the technology of using animal models of infection to assess antimicrobial activity had been called into question. [187] Once established by Linton[188] in 1977 that indeed antimicrobial resistant microorganisms from antibiotic-fed commercial farm animals could colonize the human gastrointestinal tract, the literature continually logged examples [189] of this phenomenon and even produced a molecular epidemiology of it. [190] , Holmberg synthesized critical observations on an 18-case outbreak of drug-resistant nontyphoidal salmonellosis:

1) It has been demonstrated that animals fed antimicrobics at low doses shed bacteria resistant to the ingested antimicrobics.

2) Surveys by the United States Department of Agriculture (USDA) of meat and poultry going to market show that a high proportion harbor resistant *Salmonella spp.* and other Enterobacteriaceae.

3) Resistant strains of *Salmonella spp.* are frequently recovered from humans and have increased in the 30 years during which sub-therapeutic antimicrobials have been added to beef, pork and poultry feed.

4) Several other investigators have shown that resistance (R+) plasmids extracted from *Salmonella spp.* from humans and from food animals are the same (i.e., there is substantial overlap between human and animal pools of drug-resistant *Salmonella spp.*"[191]

These observations coincide with individual observations over a great deal of the literature from the previous twenty years, including the observations of A. Ch. Sarkisov of the All-Union Experimental Veterinary Institute in the USSR (1966) cited earlier in the present investigation. The notion of antimicrobials as food supplements has even been considered for humans. In the 1950's and 1960's, a series of studies was conducted in which antibiotics (usually tetracyclines or penicillins) were administered in doses ranging from 5 mg to 100 mg per day to persons of all ages for periods of up to three years. These studies [192] indicated that minimal but measurable growth increases resulted when infants were given the supplemental antibiotics.

The investigative and evaluative powers of organized teams from various nations [193,194] have been brought to bear on antimicrobial use. The most notorious of these (England, 1960's) resulted in a series of national regulations for the use of antibiotics in animals bred for food. After a decade of being in effect, by most accounts these regulations at the least failed to accomplish what their writers originally intended. [195] The basic strategy here was to classify antibiotics into two categories, "feed" and "therapeutic." Those in the feed category had either minimal or no therapeutic role, and were

available for use in animal feeds without prescription. Therapeutic antimicrobials could be prescribed only by a medical or a veterinary practitioner, and the regulations emphasized that the veterinarians were to prescribe a therapeutic antimicrobial only if they had the animals under their care. Threlfall [196] suggested that the veterinary profession ought to show more prudence in its prescribing habit and Richmond & Linton [197] suggested that medical as opposed to veterinary use of tetracycline may have created a selective pressure for the high incidence of tetracycline-resistant organisms in the human population. The ***Swann Committee*** may have placed undue emphasis on the preservation of therapeutic usefulness of one antimicrobial agent (chloramphenicol) over others. Some other factors that may have conspired to defeat the utility of the British regulations have been identified, including:

1) The use of other drugs (such as tetracycline and trimethoprim) may have encouraged spread of resistance to chloramphenicol as part of multi-resistance.

(2) Over enthusiastic representatives of pharmaceutical firms as well as black market

operators may have found farmers all too ready to sidetrack their veterinarians.

3) Advertisements in trade periodicals may have encouraged these attitudes.

These lessons may have serious repercussions yet to be felt in medicine.

There are yet other reports in the literature asserting that the phenomenon of antibiotic resistance factors among microorganisms likely to have been minimally affected by human intervention may be linked to wild ecosystem survival. [198] Despite all of the above observations, there is little doubt that antibiotic use selects for antibiotic resistance genes (See Gardner, et al., 1969 cited earlier). Several articles [199,200] and documents [201,202] in the literature of the mid 1970's to early 1980's clearly demonstrate concern by the medical community over its liability in this problem as well as its creativity in proposing solutions in the form of proper prescribing regimens and other policies.

Effect of Clinical Misuse of Antimicrobial Agents on Resistance

It is indeed this clinical issue which constitutes the sixth and last major focal point revealed in the present review of the literature. Could clinical misuse of antimicrobial agents act as a stimulatory factor relating to antimicrobial resistance? The literature suggests that this is likely to be so in some measure. Investigations began by Louria & Kiaminski [203] lasted over a decade [204,205,206,207] and established that minimal overgrowth due to antimicrobially resistant bacteria may predictably follow from systemic antimicrobial therapy. This undesirable microbial complication may be due to direct influence of some of the agents used on the colonization resistance of the digestive tract, [208] or to the suppressive effect of the agents on endogenous microorganisms [209] or on other factors previously reviewed here. These concepts may have been developed over decades of the "antimicrobial era," but the idea that resistance was a changeable, escalating phenomenon in the health care arena was observed and reported early on.

In a series of reports [210,211] in the early 1970's, Maxwell Finland chronicled the evolving nature of antimicrobial resistance among microorganisms isolated at the Boston City Hospital since the

beginning of the "antimicrobial era." Other reports [211,213,214,215,216] clearly demonstrate that the phenomenon of drug resistance as related to agent use was well documented and probably well known to practicing physicians. During this period much has been made in the literature about ways to deal with the fact that we may be causing some of the problem. Some concern was related to the notion of initial vs. definitive antimicrobial therapy and that very different strategies need to be employed to achieve the greatest success. [217] Distinctions were also made between prescribing strategies to be used in hospital practice [218,219] and office [220] or family practice. [221] Various strategies for focused antimicrobial therapy became popular by the mid-1970's. [222]

As many of these corrective efforts evident in the literature suggested, there seemed to be no end to the responses that microorganisms would make or exhibit in their own defense. Some of these responses seemed to persist despite long standing efforts to understand and defeat them. An example is tolerance. At least a couple of forms of tolerance have been reported in the literature. The first, phenotypic tolerance, was described in 1942 [223] followed by genotypic tolerance described in 1970 [224] with continuing work reported on the underlying basic science to the present day. [225] By

the late 1970's and early 1980's so much attention was focused upon the complexity of factors to be considered in the selection of appropriate antimicrobial agents that computer models based on "expert system technology" were being developed and tested [226] as were patient-care audit [227] and computer based antimicrobial auditing systems. [228]

Despite all these controls and all the awareness that is evident in the literature, evidence has accumulated that the resistant strains that we help to create [229] in our health care facilities do in fact escape from facilities and are distributed to the surrounding environs. [230] The third generation cephalosporins offer an example of another problem in this arena. In the ever escalating effort to produce more and newer [231] antimicrobial agents, did the technology of development and production outstrip the science necessary to understand and evaluate these agents adequately? Some of the evidence summarized in 1983 by Sanders [232] suggests that this dichotomy may be so. New relationships between ß-lactamases and ß-lactam antimicrobial agents have been reported [233,234] (such as lactamase induction depression) that place even more emphasis on correct clinical use. The very proximal process of treating a patient in a temporal sense has been affected by the phenomenon of drug

resistance emerging during antimicrobial therapy [235] as has been reviewed earlier. This problem is made even more troublesome by the fact that some of the newer organism-agent resistance relationships are not easily detectable by state-of-the-art laboratory tests. [236,237] This problem, of course, leads to more prescribing of these agents with unpredictable success followed by subsequent higher doses and the escalation continues.

Thus there appears to be evidence in the accumulated literature on these matters leading us to understand that antimicrobial resistance is very wide ranging, of long duration (both prior to, and during the "antimicrobial era"), has been contributed to by early prophylactic prescribing practices, has evolved in complexity from chromosomally mediated to plasmid mediated, has been measurably affected by non-medical use of antimicrobial agents and is contributed to by clinical misuse.

Chapter III

Hypothesis

As the cephalosporin amount increases, *Streptococcus faecalis* resistance increases at least as fast. Based on the review of literature, all factors affecting stimulation of antimicrobial resistance should be considered and reflected in the data of overall resistance.

Definition of Terms

Abuse of antimicrobial/antibiotic agent:

A general level of production and antibiotic agent consumption of an agent that results in long term stimulation of high levels of resistance to those agents not in the best interest of consumers of the agent.

Antibiotic:

A chemical substance produced by a microorganism which, in dilute solutions, has the capacity to inhibit the growth of or to kill other microorganisms.

Antimicrobial:

An agent that kills microorganisms or suppresses their multiplication or growth.

Appropriate antimicrobial/antibiotic use:

Justifiable administration of an agent with regard to the clinical situation and current medical practice.

cephalosporin level:

The annual dry weight production (adjusted for population changes based upon an index year of 1971) available in the U.S.

cephalosporin resistance:

Zone sizes by standard disc diffusion susceptibility tests reported by diagnostic microbiology laboratories as indicating *in vitro* contraindication of use.

Inappropriate antimicrobial/antibiotic use:

Administration of one agent when a more effective, a less toxic or less expensive agent is recommended by current medical practice; or when improper dosing or administration intervals is prescribed.

Streptococcus faecalis:*

A Gram-positive cytochrome-negative, coccoidal bacteria characterized by the following attributes:

Catalase	-
Hemolysis (5% SRBC in TSA)	v
Streptococcal group Antigen	D
Hydrolysis of Bile Esculin Agar	+
Growth in 6.5% NaCl	+
Bile solubility	-
Growth at 10°C.	+
Pyruvate	+
Arginine	+,oe
Starch	-
Hippurate	v
Sucrose	+,oe
Lactose	+,oe
Mannitol	+
Sorbitol	+,oe
Arabinose	-,oe
Sorbose	-
Inulin	-
Raffinose	-,oe
Gluccan	N

+ = 90% or more of strains positive
- = 10% or less of strains positive
D = one of the Lancefield Categories
V = variable reactions
oe = occasional exceptions from the state reactions
N = no glucans

*The epithet of this organism was changed in common usage in the late 1980's to *Enterococcus faecalis*. It has been used in this form for this study in consideration of the vast preponderance of literature referring to it as such.

Unjustified antimicrobial/antibiotic use:

Administration of any agent when there is no clinical indication or when excessive duration is prescribed.

Assumptions

1. Abuse of antimicrobial agents is widespread.

2. The sheer quantity of antimicrobials available to the environment through human-directed production in exaggerated comparison to the amount that would have been produced by natural biosynthesizing organisms is stimulus enough to the microbial pool to encourage emergence and frequency of genetic protective mechanisms.

3. The "amount" of cephalosporin available to the environment can be objectively estimated by production and certification figures and marketing research estimates. These figures

are only estimates in that production sent to other countries cannot always be identified.

To the extent that the hypothesis has been established, resistance should be a reflection of the total Darwinian pressure for allelic selection. The most appropriate data gathering technique then is to quantify the gross production of cephalosporin and graph it superimposed on the resistance profile over time exhibited to it by *Stp. faecalis* .

Scope and Limitations

While the data on the general subject of this study is abundant, it tends to be discrete, noncontinuous and unpredictably available over long periods of time. Therefore, a single organism with limited target organ specificity and reasonably stable epithet designation over time has been selected and, likewise, the agent selected has continuous utilization over the span of the study with accompanying standard usage patterns. Nonetheless, precise data has been difficult or impossible to come by for some or several index points for each of these two analytes.

Procedure

Sources of Data

The primary documents of data have been the national incidence of resistance to cephalosporin exhibited by *Streptococcus faecalis* as recorded by the National Technical Information Service, the United States International Trade Commission and other national data bases. cephalosporin quantity data have been determined by production and certification figures and marketing research estimates obtained from U.S. manufacturers of cephalosporins and compiled by various federal agencies such as the U.S. International Trade Commission.

Independent variable

In this study the level of availability (production) of cephalosporin has been viewed as the predictor or independent variable of resistance. This research study views availability of drug as a cause, results being dependent upon differences of level of the independent variable.

Dependent Variable

Microbial resistance levels are viewed as the dependent variable because they should vary in some relationship to the independent variable (availability).

Intervening Variable

Changes in prescribing protocols are viewed as intervening variables because their effect would be to influence the relationship between the independent variable (availability) and the dependent variable (resistance).

Statistical Hypothesis

High levels of availability (production of cephalosporin) will result in high levels of resistance on the part of *Streptococcus faecalis*.

Data Gathering

Review of the primary documents (from US manufacturers and CDC) has been utilized to gather data for the study.

Data Analysis

The gaps in available data and the change in reporting and reviewing practices over the span of this study have obviated several types of data analysis. The array and depth of data has been sufficient for graphical analysis and is compelling. Conclusions can be drawn from several graphical presentations in Chapter IV.

Chapter IV

Results

Enterococci (to include *Stp. faecalis*) are important nosocomial pathogens accounting for up to 10% of all infections among hospitalized patients in the U.S .[238] Estimates indicate that the number of serious enterococcal infections increased 20% per year from 1976 to 1981 and continues to increase. [239,240, 241,242] By the late 1970's such high doses of Cephalothin and related agents were being used to effect favorable clinical outcomes that quite serious ADR's (adverse drug reactions) were becoming common enough to report on in the literature. [243] The hope that *Streptococcus* (*Enterococcus*) *faecalis* would not fall in line with so many other ß-lactam treated invading microorganisms such as *Sth. aureus* and Gram-negative bacilli was shattered in 1983 with the discovery of a ß-lactamase producing strain in Houston, Texas [244] that turned out to be plasmid dependent and of staphylococcal origin. [245] This observation quickly brought *Stp. faecalis* into the same sphere of consideration as many other infectious bacterial agents commonly treated with ß lactam agents. In particular this organism had a long relationship chemotherapeutically with Cephalothin, a popular and successful ß-lactam agent.

The hypothesis of the present study assumes that there has been an increase in antibiotic production over time that would contribute to the Darwinian pressure to increase any antimicrobial allelic or plasmid-derived resistance to such agents as organisms might be exposed to.

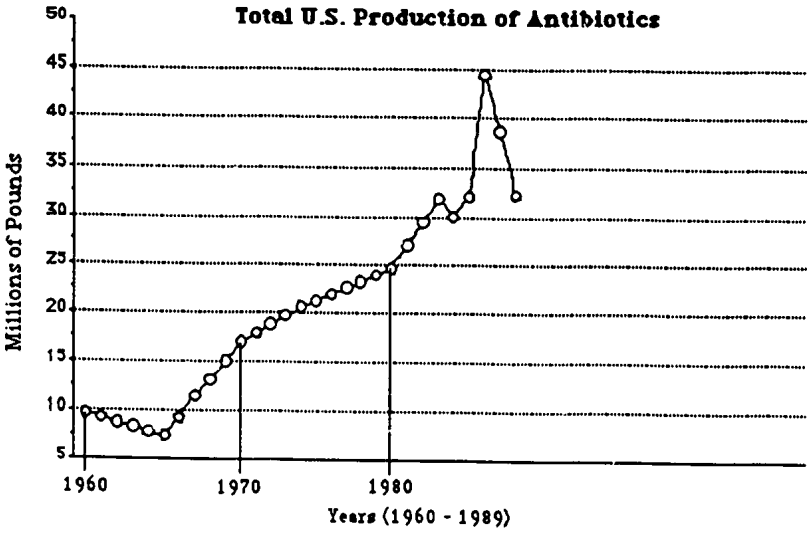


Figure 1.

Figure 1 indicates that just such an event has occurred at least as regards U.S. total production of antibiotics over the nearly thirty year period 1960-1988. This period showed a 256% increase overall (389% increase for 1960-1986) with the most steady and sustained increase occurring from the period after the passage of Medicare and

other access-enhancing legislation of the 1960's. While the total production of medicinal chemicals in the U.S. has not been consistently reported, the total antibiotic production has, as in Figure 2.

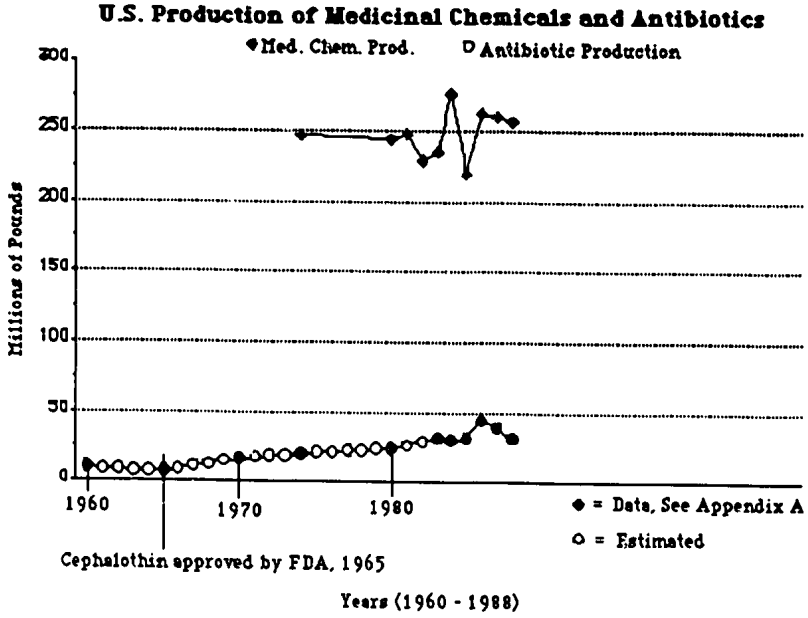


Figure 2.

It would appear from the limited data available that a rough parallel between medicinal chemicals of all types and antibiotics exists. Cephalothin, the first widely available cephalosporin was released in 1965 by the United States Food and Drug Administration (USFDA)

and began to be monitored carefully in terms of total production in 1971. When compared to total antibiotic prescriptions, there is a production parallel as in Figure 3.

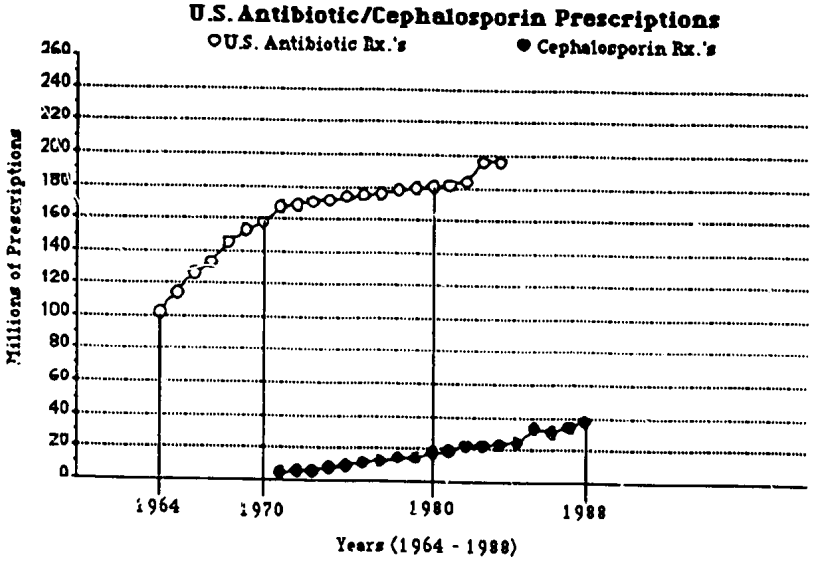


Figure 3.

From this data, if the total cephalosporin prescription amount is segregated (Figure 4) it indicates the same kind of increase as in the total antibiotic production (Figure 1). To this extent it seems safe to conclude that number of prescriptions of a particular agent (at least in this case) parallels the total production in pounds. The fact that

this comparison must be made for the purposes of this study is a commentary on the true scope of the antimicrobial use-resistance problem in the United States and worldwide. Despite the sizable economic impact of these agents ($75 billion in 1980, $150 billion in 1990 and an estimated $270 billion by 2000 worldwide [246]), data is still collected sporadically on their production and sales. In addition, we are just beginning to appreciate that there is a disparate distribution of these agents for all uses between developed and developing nations. While the developed countries (U.S., Canada, Japan and Western Europe) represent 15.9% of the world population, they account for 51.9% of world sales and, by comparison, the 74.5% of the world population living in Africa, the Middle East, Latin America and Asia only account for 21.0% of world pharmaceutical sales. [247] In addition to the fact that our proportional overabundance of these agents occasionally results in literal overdoses, [248] it also affects the global resistance plasmid flow in ways that can only be imagined at this juncture of our knowledge.

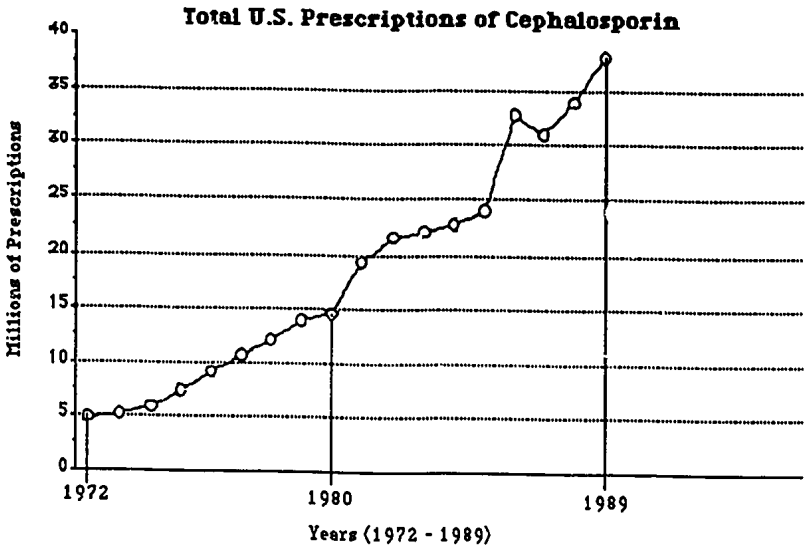


Figure 4.

Further, it would seem that this rate for Cephalothin at least and perhaps for other antimicrobial agents exceeds the prescription pattern of chemotherapeutic drugs in general as in Figure 5. Indeed it appears that the sporadic and uneven world production data that is interpretable suggests that cephalosporins have consistently represented about 12% of total antibiotic production and use and currently are at about 1,200 - 1,400 tons annually.[249,250]

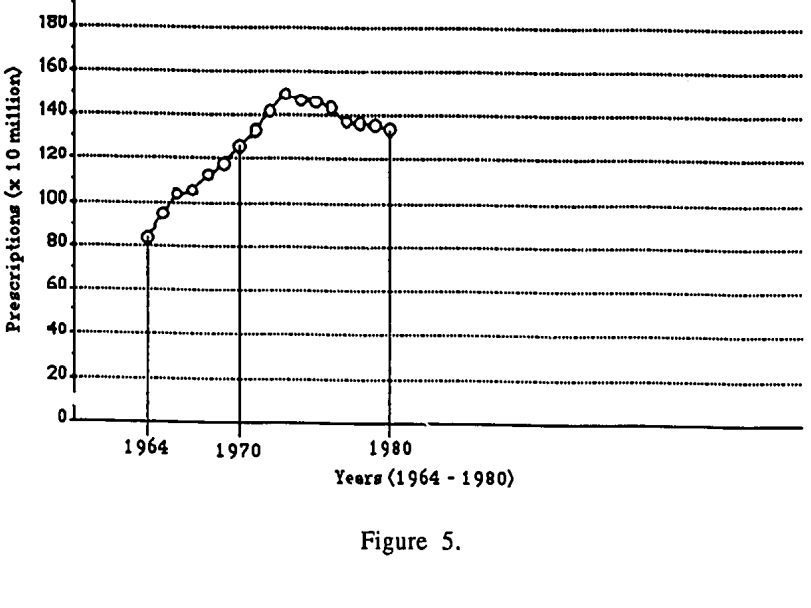


Figure 5.

Over this same period of time, the response by *Stp. faecalis* to the increased presence of this agent, as for many others, has produced a percent sensitive decline from roughly 62% to 18% as in Figure 6 (page 47). The cross species and even cross genus [251] sharing of resistance plasmids reviewed in Chapter IV may well have had an effect on the slope of this curve especially since 1978. During this time interval, Cephalothin was the lead cephalosporin in production the world over except for the last couple of years when other agents in this group and other groups of ß - lactam and other agents began

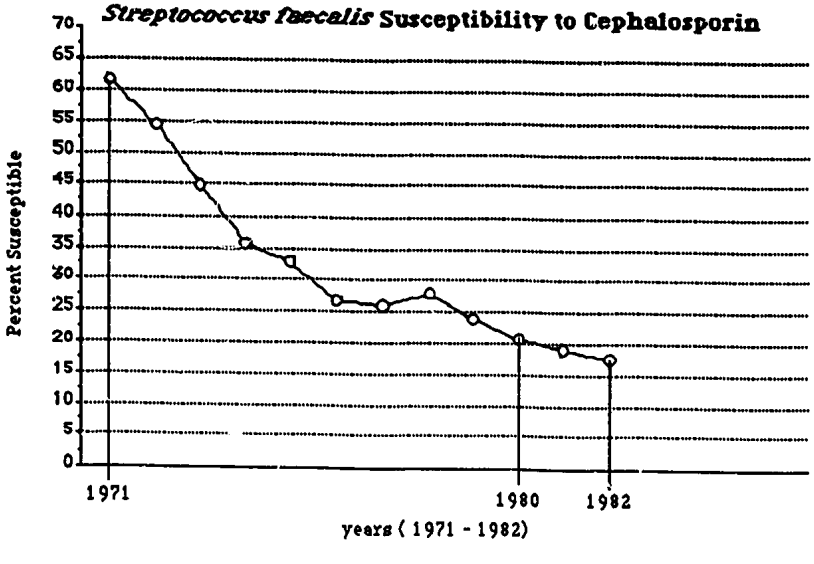


Figure 6.

to replace it in prescribing protocols. [252] In fact this practice of defining the standard prescribing protocols for various "drug-bug" combinations quite popular in the 1960's and 1970's began to fade in the 1980's as they had to be revised so frequently and had to be of such immense detail as to be of less and less use.

When the data sets from Figures 4 and 6 are superimposed, as in Figure 7 (page 48), they show an obvious relationship.

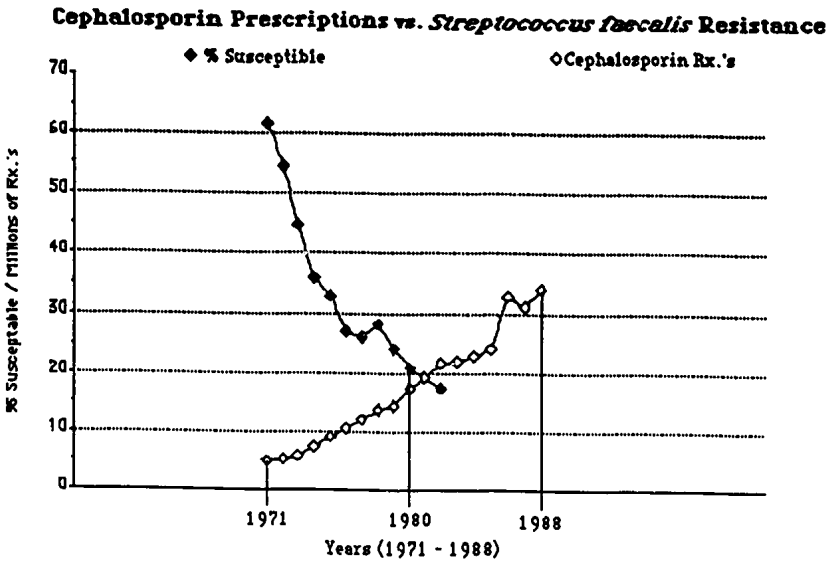


Figure 7.

In the span of this collective data set, despite early [253] (1950's) knowledge of this organism's quick response to chemotherapeutic challenge and continual revelations about the organisms resistance process [254] and general epidemiologic attributes, [255] entrenched prescribing patterns persisted (as was true of many other "drug-bug" combinations) to the point of a lack of use of the antimicrobial agent. Other agents were discovered [256] and introduced[257] in such a way that Cephalothin became less and less prescribed by prescribing physicians in response to infectious disease challenges posed by *Stp. faecalis.* [258] To this end the data collection on one arm of the data set

arrayed in Fig 7 ends abruptly. This situation, repeated in various ways for other "drug-bug" combinations given the collective pressures of prescribing practices, pharmaceutical production investment and the lag of research on resistance, has resulted in making it difficult or unlikely to be able to do such a longitudinal study as the present one with "drug-bug" combinations of the 1990's and beyond. Nonetheless, the information revealed by the data flow culminating in Figure 7, is clear and compelling. As Cephalothin was produced in ever increasing quantities, its effectiveness as a chemotherapeutic agent in the treatment of *Stp. faecalis* induced infectious disease in humans was diminished.

Chapter V

Long Range Consequences

The results of this study are consistent with its hypothesis. They illuminate corrective action to resolve a serious problem, that is to say reducing the amount of antimicrobial available to the environment by proper medical use, decreased agricultural prophylactic use, etc., would result in a concurrent reduction in the Darwinian pressure propagating high densities of drug resistant plasmids. The possibility for change in the existing social system is quite real and of significant magnitude. The various changing dynamics of non-medicinal and medicinal antimicrobial agent use as a possibility of course must be taken into account. An example of this is indicated in Figure 8. The literature is convincing on the point that our use of antimicrobial agents does have an effect on microbial resistance to these agents. The data in this study shows clearly that not only does our method of using these agents result in their declining efficacy but almost in direct parallel to the quantity of our use. Continued misuse of these agents seems to be irresponsible. Previous work in this field, such as that by Smith, et. al. (See Ref. #38) suggests that at a minimum, we should try to use these agents when their use is required rather than when it is expedient.

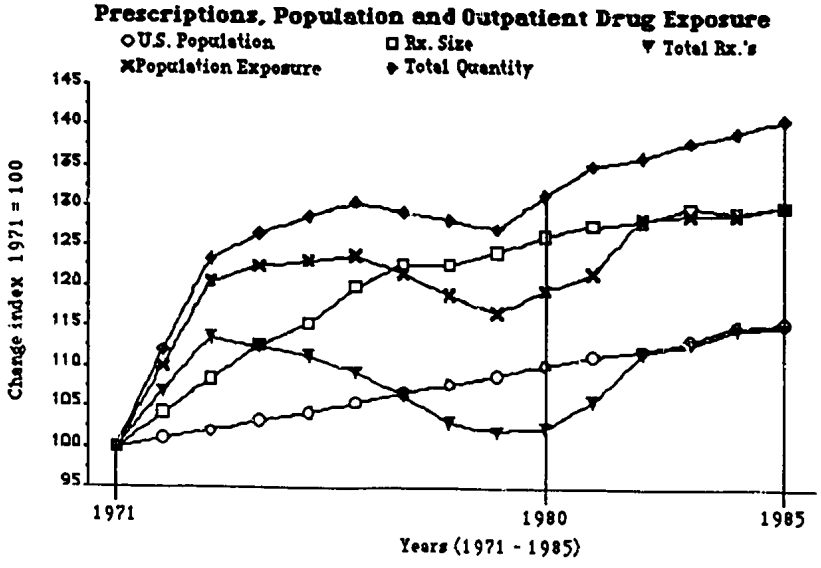


Figure 8.

This data reveals a change in the relationship between prescription frequency and total population exposure to chemotherapeutic agents in the U.S. Traditionally, the number of prescriptions paralleled the total population exposure to chemotherapeutic drugs, but in the early 1970's the total number of prescriptions fell as the prescription size continued to grow. This growth in the size of prescriptions (number of tablets, injections, capsules, spoonful, etc. per prescription event) offset the decrease in numbers of prescriptions enough to keep the total population exposure increasing for several years. This

phenomenon has continued to evolve to the current time where total prescriptions and total population exposure are now again increasing at a similar rate.

Yet another factor to be considered relates to the rapid change now necessary in the organism-agent treatment regimens. For example, the organism in this study is now considered to be inherently resistant to multiple antimicrobial agents, including polymyxins, lincloseamides and trimethoprim-sulfamethoxazole and as having reduced susceptibility to cell wall agents such as ß-lactams and vancomycin. [259] The latest escalation in the confrontation between prescribing practices and microbial genetics as regards this microorganism, involves synergistic combinations of a cell wall active agent plus an aminoglycoside. [260,261] Even in these regimens the organism eventually breaks out on top with what is now described as High Level Gentamycin Resistance (HLGR) and High Level Streptomycin Resistance (HLSR) toward the aminoglycoside partner in the antimicrobial cocktail with resulting loss of synergism. [262] With the subject microorganism of this study now well appreciated as multi-drug resistant, these problems along with the $100 million to $30 billion [263] incremental cost associated with antimicrobial resistance annually in U.S. hospitals alone is cause for social change.

At this point, the literature and production figures may not suggest the same conclusion for all organism-agent combinations, but a common conclusion may be possible. [264] It is quite likely that there are more and more complicated factors at work in the dynamic of other organism-agent relationships. [265] What this study helps to demonstrate is that evaluation from a long perspective is illuminating, that further study in this arena is likely to be productive, and that the resultant social change that might follow could be part of the permanent relationship [266] between us humans and our microbial companions in evolution. Some social change strategies that appear germane to the problem at hand include:

1) Curtail or abandon antimicrobial use

Even though the literature clearly suggests that antimicrobial resistance among microorganisms subsides over time when antimicrobial agent use is minimized or discontinued, this is just not a practical solution in general. However, in circumstances that are desperate on a local level or unexplainable by other scenarios or both, this notion should be kept in reserve.

2) Prevent acquisition of resistance

One of a number of possible reviews of this matter has been conducted in Chapter III of this study suggesting that creating the Darwinian pressures for plasmid-based resistance practically ensures their increase in the microbial gene pool. Even the once-thought barrier of cross-species or cross-genus sharing of these bits of DNA are apparently no longer a matter of anticipated safety. To the extent, however, that other research in this field may reveal some inhibitable cell-cell or cell-surface property essential or contributory to such genetic transfer, a solution at this level may some day be at hand.

3) Proliferation Prevention Within an Individual

The major recommendation of this study must relate to proper use of existing antimicrobial agents and maximizing the contemporary agent-organism competitiveness. These steps seem obvious from the standpoint of minimization of resident flora depression so as to enhance competition between drug-resistant invaders and host microorganisms. The possibility of self/non-self microbial vaccine cannot be ruled out.

4) Prevention of Proliferation Between Individuals

This idea actually has a long [267] and quasi-successful history relative to this problem and may yet produce new solutions. The 1940's "barrier-strategy" was born of the challenge posed by *Stp. pyogenes* and the shrapnel bombs of World War II. The idea in these cases was to erect a physical or fomite barrier between the infectious disease patient and everyone else. The "filtration-strategy" followed *vis-a-vis* airborne *Staphylococcus spp.*, whereby microorganisms likely to be aggressive in an infectious disease sense needed to be plucked out of floating proximity of the patient. The "opportunity-minimization strategy" was attendant to the 1970's problem of Gram-negative bacillus resistance. Observations were made that infectious disease jeopardy with drug-resistant microorganisms was due in part to opportunity. The use of indwelling urinary catheters frequently results in infection within 48 hours. Reducing unnecessary catheterization reduces infection and antimicrobial resistance. The most contemporary challenge is the multiple-drug resistant microbial invader and this circumstance has again suggested an "environmental/people flow" response. All these historic and current notions having a bearing on preventing cross contamination with drug-resistant microorganisms should continue to be explored as social change options.

5) Agricultural management

There are, of course, several obvious parameters extant in our non-medicinal use of antimicrobial agents that bear on the overall problem of resistance. The nature of contact between animals in their feed-lot, habitat and slaughter-house environments, contact with feces and general agricultural hygiene are all material to the constellation of solutions needed to address this problem. Also suggestive of societal-business actions would be matters of how lost/sold animals from one farming location are replaced, from how diverse a group of suppliers and how diverse the customer base those suppliers have. These all relate to a defined technology already existing in their field called Relocation-Mixing-Dietary (RMD) syndrome.

6) Antimicrobial Use and Resistance Data Collection

The standard indexing for measuring drug use in each nation should be given significant consideration. The Norwegian originated Defined Daily Dose (DDD) index [268] would provide a basis for national and world evaluation and comparison of segmental data. If this were to be coupled with the liberation of currently privately collected data in this field, then the great possibility for more light to shine upon this problem would be greatly enhanced.

In all probability the tremendous but stepwise modifications in federal, state and other health policy, as well as policy decisions and incentives in the United States Department of Agriculture and elsewhere, have conspired to produce the various direction changes evident in Figure 8. Many experts in the general arena of health care have suggested that this imprecise and politically susceptible approach has resulted in glaring loopholes in reimbursement procedures for the federal and state governments as well as the over 1,500 health insurance agencies in the United States.

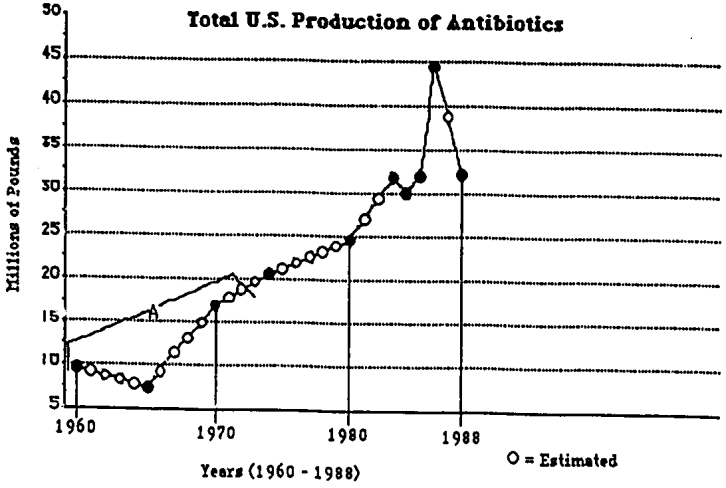
These data revealed in the present study suggest that national (or global) attitude changes would likely have a long term beneficial effect on the deteriorating circumstances surrounding microbial resistance to antimicrobial chemotherapeutic agents. Basically this would involve all of us looking at the "drug-bug" interface as a microscopic representation of the whole earth environment that has been examined stringently of late. The same type of policies and awareness need to emerge in the chemotherapeutic world. That is, we must all use the resources at hand in a thoughtful and responsible manner.

From once thinking of antibiotics as exceptional agents of prophylaxis to recognizing their limitations if used in that manner, we have come far. The task now is to make some permanent system-wide advance based on this lesson that may have been learned.

Appendix A

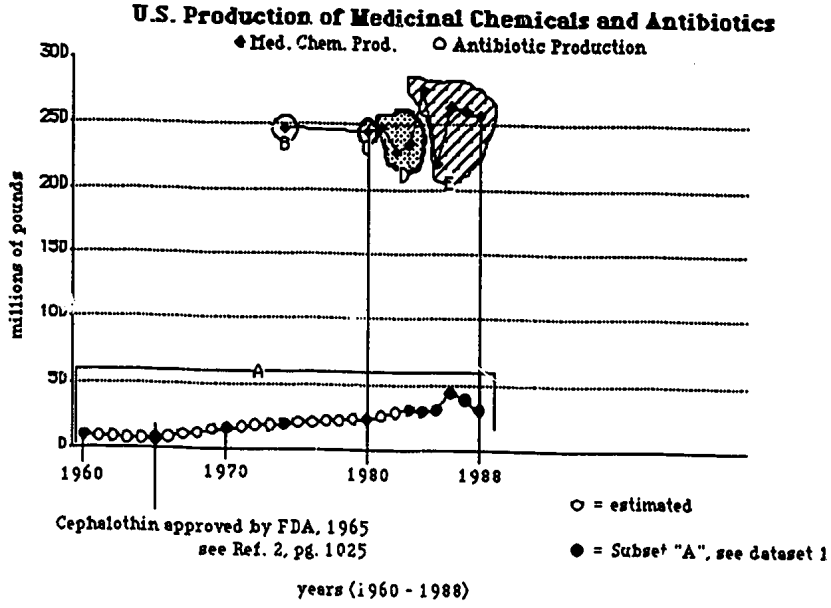
The following "Datasets" are provided in order to clarify the origin of various data presented in Chapters IV and V. Most data points are ultimately referenced to original sources listed in Appendix B.

Dataset #1 (Figure 1.)



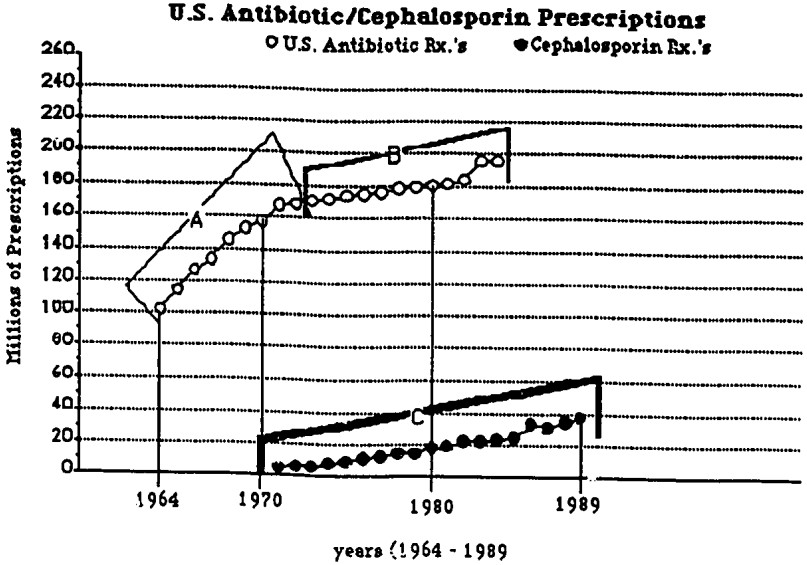
- 1974 20.549 million pounds see Ref. 269,
- 1980 24.628 " " see Ref. 270,
- 1983 31.886 " " see Ref. 271
- 1984 30.442 " " see Ref. 272
- 1985 31.992 " " see Ref. 273
- 1986 44.430 " " see Ref. 274
- 1988 28.827 " " see Ref. 275

Dataset #2 (Figure 2.)



B	1974	243.543 million pounds	see Ref. 276 p. 95
C	1980	243.876 " "	see Ref. 277 p 117
D	1981-3		see Ref.#278p. 97
E	1984-8		see Ref.#279

Dataset # 3 (Figure 3.)

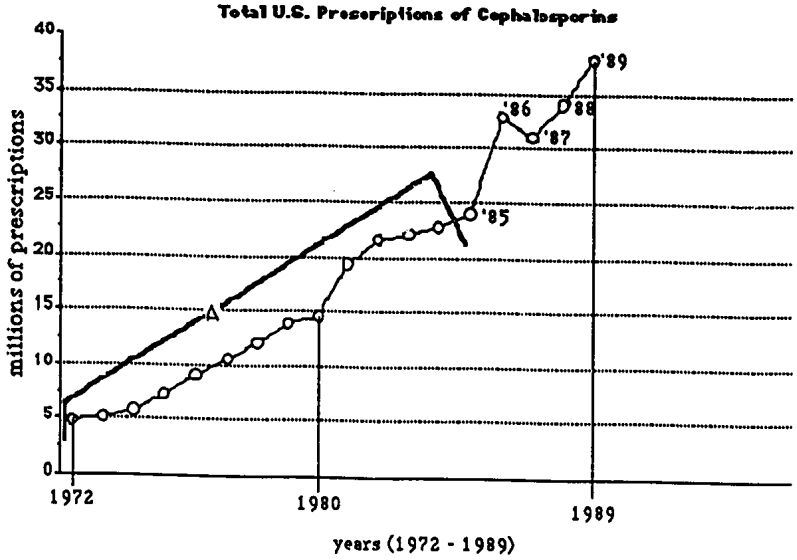


Subset "A" see Ref. 2, pg. 1025

Subset "B" IMS America, Ambler, Pa., 1985

Subset "C" see Dataset #4

Dataset #4 (Figure 4)



Subset "A" see Ref. 280, p. 2

1985 see Ref. 281, p. 8

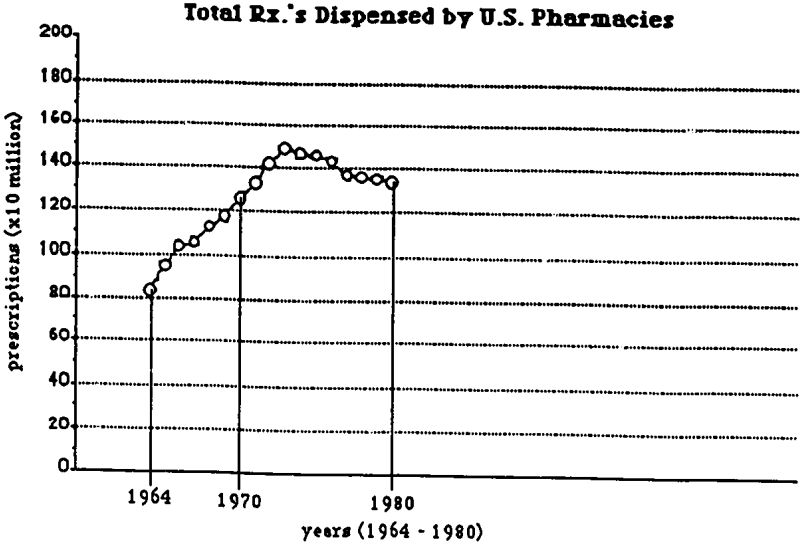
1986 see Ref. 282, p. 6

1987 see Ref. 283, p. 11

1988 see Ref. 284, p. 8

1989 see Ref. 285, p. 9

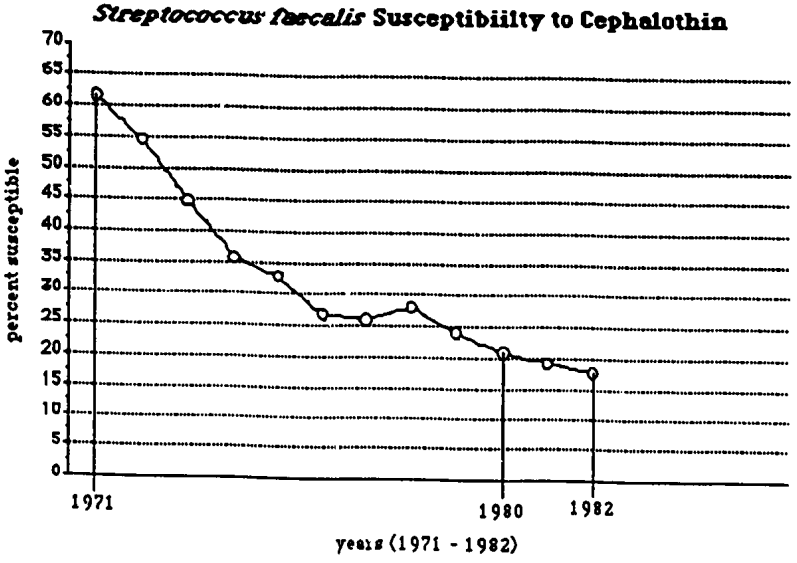
Dataset #5 (Figure 5.)



see Ref. 285, pg. 7

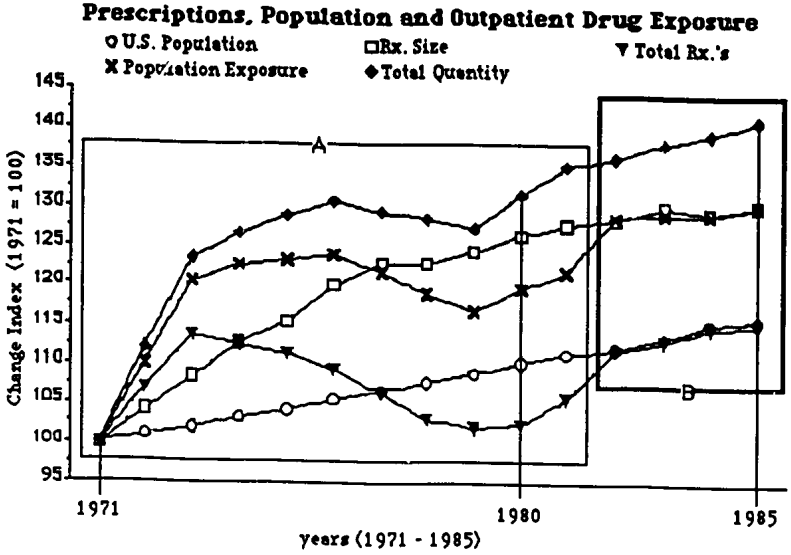
1964	836.4	million	prescriptions	dispensed
1965	945.5	"	"	"
1966	1034.5	"	"	"
1967	1056.4	"	"	"
1968	1127.3	"	"	"
1969	1174.6	"	"	"
1970	1260.0	"	"	"
1971	1327.3	"	"	"
1972	1420.0	"	"	"
1973	1492.7	"	"	"
1974	1472.7	"	"	"
1975	1463.6	"	"	"
1976	1432.7	"	"	"
1977	1374.5	"	"	"
1978	1367.3	"	"	"
1979	1354.5	"	"	"
1980	1341.8	"	"	"

Dataset # 6 (Figure 6.)



see Ref. 286, p. 793

Dataset # 7 (Figure 8.)

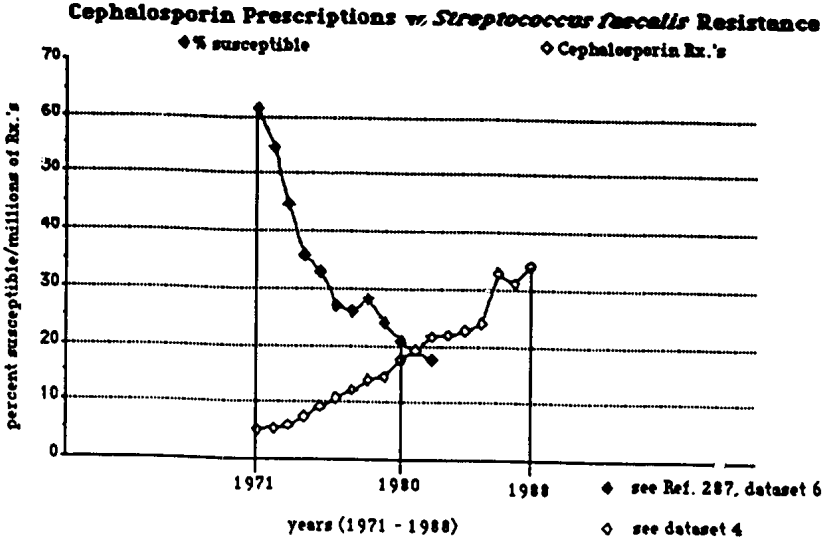


Subset "A" see Ref. 287, p. 7 (1-4)
Subset "B" see Ref. 288, p. 11(1-15)

Year	US Population	Rx. Size	Total Rx.'s	Population Exposure	Total Quantity
1971	100	100	100	100	100
1972	101	104.2	106.9	110.1	112
1973	102	108.4	113.6	120.5	123.5
1974	103.2	112.7	112.4	122.5	126.7
1975	104.3	115.3	111.4	123.3	128.9
1976	105.6	120	109.3	124	130.7
1977	106.6	122.7	106.4	121.7	129.4
1978	107.7	122.9	103	119.1	128.4
1979	108.8	124.3	102	116.8	127.3
1980	110.3	126.3	102.5	119.7	131.6
1981	111.4	127.7	105.8	121.7	135.1
1982	112	128.4	111.8	128.6	136.2
1983	113.4	130	113	129	138
* 1984	115.1	129.2	114.8	129.1	139.1
1985	115.7	130.3	114.9	130.2	141

* = reference point, see Ref. 289, p. 1041 U.S. Population = 234,443,000

Figure 7.


Cephalosporin Prescriptions vs. Streptococcus faecalis Resistance
◆% susceptible
◇ Cephalosporin Rx.'s
percent susceptible/millions of Rx.'s
70
60
50
40
30
20
10
0
1971
1980
1988
years (1971 - 1988)
◆ see Ref. 287, dataset 6
◇ see dataset 4

Appendix B

1 Great Britain Army Medical Directorate.*Penicillin Therapy and Control Manual Introduction*. London: 21 Army Group. 1945: 3-5.

2 Simmons HE, Stolley PD.This is Medical Progress? Trends and consequences in antibiotic use in the United States. *JAMA* 1979: 9: 1023-1028.

3 Mead PB. Prophylactic Antibiotics and Antibiotic Resistance (Review). *Semin Perinatol* 1977: 1(1): 101-11.

4 Barriere SL, Conte JE Jr. Emergence of Multiple Antibiotic Resistance During the Therapy of *Klebsiella pneumoniae* Meningitis. *Am J Med Sci* 1980: 279(1): 61-65.

5 Casewell MW, Phillips I. Aspects of the Plasmid-Mediated Antibiotic Resistance and Epidemiology of Klebsiella Species. *Am J Med* 1981: 70(2): 459-62.

6 Boyce JM. Increasing Occurrence of Methicillin-Resistant *Staphylococcus aureus* in the United States. *Infect Control* 1982: 3(5): 377-83.

7 Watanabe T. The Origin of R Factors. *Ann NY Acad Sci* 1971: 182: 126-40.

8 Young FE, Meyer L. Genetic Determinants of Microbial Resistance to Antibiotics. *Rev Infect Dis* 1979: 1: 55.

9 Kunin CM,Tupasi T, Craig WA. Use of antibiotics: A brief exposition of the problems and some tentative solutions. *Ann Int Med* 1973: 79: 555-60.

10 Check WA. How to affect antibiotic prescribing practices. *JAMA* 1980: 244: 25594-5.

11 Devriese LA. Sensitivity of staphylococci from farm animals to antibacterial agents used for growth promotion and therapy: A ten year study. *Ann Rech Vet* 1980: 11(43): 399-408.

12 Finland M. Emergence of antibiotic resistance in hospitals. *Rev Inf Dis* 1979: 1: 4-21.

13 Great Britain Army Medical Directorate. *Penicillin Therapy and Control Manual*. London: 21 Army Group. 1945: 13-14.

14 Waksman SA. *Streptomycin: Nature and practical applications*. Baltimore, Maryland: Williams and Wilkins, 1949.

15 Fain S.The Bottom of the Antibiotic Box, *Med J Aust* 1977: 2(4): 109-11.

16 Alford RH. Infections Due to Endemic Multiply Resistant Gram-Negative Rods: Sensitivity to and Therapy with Cefoxitin. *Rev Inf Dis* 1979: 1: 175-182.

17 Beneveniste R, Davies J. Mechanisms of Antibiotic Resistance in Bacteria. *Ann Rev Biochem* 1973: 42: 471.

18 Cohen ML, et al. Common R-Plasmids in *Staphylococcus aureus* and *Staphylococcus epidermidis* during a Nosocomial *Staphylococcus aureus* Outbreak. *Antimicrob Agts Chemother* 1982: 21(2): 210-5.

19 Finland M. Changing Patterns of Susceptibility of Common Bacterial Pathogens to Antimocrobial Agents. *Ann Inter Med* 1972: 76: 1009-36.

20 Finland M, Murray R, Harris HW, et al. Development of Streptomycin Resistance During Treatment. *JAMA* 1946: 132: 16-21.

21 Godfrey AJ. ß-Lactam Resistant *Pseudomonas aeruginosa* with Modified PBP's Emerging During Cyctic Fibrosis Treatment. *Antimicrob Agts Chemath* 1981: 19(5): 705-11.

22 Locksley RM, Cohen ML, Quinn TC, et al. Multiple Antibiotic-Resistant *Staphylococcus aureus*: Introduction, Transmission, and Evolution of Nosocomial Infection. *Ann Int Med* 1982: 97(3): 317-24.

23 New HC. The Emergence of Bacterial Resistance and its Influence on Empiric Therapy. *Rev Inf Dis* 1983: 5(5): 59-20.

24 Widemann B. Development of Bacterial Resistance to Antibiotics. in Girldroni G, Grass I, and Sabath LD (ed) *New Trends in Antibiotics: Research and Therapy*, North Holland: Elsevier. 1981.

25 Abramowitz PW, Nold EG, Hatfield SM. Use of Clinical Pharmacists to Reduce Cefamandole and Ticarcillin Costs. *Am J. Hosp. Pharm* 1982: 39(7): 1176-80.

26 DiPiro JT, Kilsdonk GF, Amerson AB, et al. Factors Potentially Influencing Aminoglycoside Use and Expenditure. *Am J. Hosp. Pharm* 1982: 39(7): 1180-3.

27 Durbin WA Jr, Lapidas B, Goldman DA. Improved Antibiotic Usage Following Introduction of a Novel Prescription System. *JAMA* 1981: 246(16): 1796-800.

28 Scheife RT, Tally FP, McGowan K et al. Cost Comparison of Two Antimicrobial Regimens for Treating Mixed Aerobic-Anaerobic Infections. *Am J Hosp Pharm* 1981: 38: 1466-9.

29 Washington JA 2nd. Antibiotic Tolerance (Letter). *Ann Int Med* 1981: 95(5): 657-8.

30 Grunt J, Kremery V, Rosival L. Prophylactic use of restricted antibacterials in Czechoslovakia. *A Jour Hosp Pharm* 1982: 39: 1678 - 80.

31 Great Britain Army Medical Directorate.*Penicillin Therapy and Control Manual Introduction*. London: 21 Army Group. 1945: 3-5.

32 Finland M. Emergence of Antibiotic-resistant Bacteria. *N Engl. J Med* 1955: 253: 909-22.

33 Dowding J, Davis S. Mechanism and Origins of Plasmid-Determined Antibiotic Resistance; in: Schlessinger, D. *Microbiology*. Washington, DC: American Society of Microbiology. 1975.

34 Cohen SN, Chang ACY, Hsu C, et al. Nonchromosomal Antibiotic Resistance in Bacteria: Genetic Transformation of *Escherichia coli* by R-Factor DNA. *Proc Natl Acad Sci* USA 1972: 69: 2110-4.

35 Armstrong JL, Shigeno DS, Calomiris JJ, et al. Antibiotic-Resistant Bacteria in Drinking Water. *Appl Environ Microbiol* 1981: 42(2): 277-83.

36 Holmberg SD. Drug-Resistant Salmonella Species from Animals Fed Antimicrobials. *Inf. Dis News* 1986: 5(4): 25-8.

37 Sarkisov A. The Problem of the Non-Medical Use of Antibiotics in: Herold, Milos and Zdener, Gabriel, (ed). *Antibiotics-Advances in Research Production and Clinical Use*. London: Butterworths. 1966.

38 Smith JW, Jones SR. An education program for the rational use of antimicrobial agents. *So Med J* 1977: 70:2, 215 -18.

39 Pegg SP, et al. Changing patterns of *Pseudomonas aeroginosa* antibiotic sensitivity. *Burns Incl Therm Int* 1982: 34 (1): 31-6.

40 Hughes VM, Datta N. Conjugative plasmids in bacteria of the 'pre-antibiotic' era. *Nature* 1983: 302(5910): 725 - 6.

41 Witte W, Klare I. Frequency of Antibiotic Resistance: German Democratic Republic. *APUA News* 1987: 5(1): 1-3.

42 Goodwin CS, Hill JP. ß-Lactamaze Resistance of Cephazolin and Other cephalosporins. *Scott. Med J* 1976: 20(5): 236-9.

43 Andrews J, Bywater MJ, Emmerson AM, Keane C, Reever DS,Wise R. The Prevalence of Ampicillin, Cephalosporin and Sulphonamide Resistance Amongst Urinary Tract Pathogens. *Scott Med J* 1976: 20(5): 232-5.

44 Davidson S. Comparative Susceptibilities of 40 Strains of *Pseudomonas aeruginosa* to 10 Antipseudomonal Antimicrobial Agents. *Isr J Med. Sci* 1982: 18(8): 859-62.

45 Sogaard H. Incidence of Antibiotic Resistance and Transmissible R-Factors in the Gram-Negative Bowel Flora of Hospital Patients on Admission. *Scand J Infect. Dis* 1975: 7(4): 253-8

46 Coticelli AS, DiNino GF, Gatti M, et al. Intensive Care Units as a Source of Methicillin-resistant *Staphylococcus aureus*. *Microbiologia* 1987: 10: 345-51.

47 Aswapokee N, Vaithayapichet S. Consequences of Inappropriate Hospital Use of Antibiotics in Thailand. *APUA News* 1990: 8(2): 1-5.

48 Shlaes DM, Al-Obeid S, Gutmann L. Enterococcal Resistance to Vancomycin and Teicoplanin. *APUA News* 1989: 7(4): 1-4.

49 Tupasi TE, DeLeon LE. Rationalizing Antimicrobial Use in Respiratory Infection: The Philippines. *APUA News* 1987: 5(3): 1-6.

50 Méndez JLM, Baquero F. Genetic Linkage of Antibiotic Resistance and Bacterial Virulence. *APUA News* 1988: 6(3): 1-3.

51 Kafle KK, Rajbhandary SM, Acharya SM. Hospital Use of Anti-Infectives in Nepal. *APUA News* 1989: 7(4): 1-3.

52 Sköld OA. New Enzyme for Trimethoprim-Resistance Found in Sri Lanka. *APUA News* 1987: 5(2): 1-3.

53 Turcu T, et al. The Recent Aspects of Gp. D. Streptococcal Sensitivity to Antibiotics. *Arch. Roum. Pathol. Exp. Microbiol* 1981: 40(3): 199-204.

54 Riley I, Carrad E, et al. The Status of Research on Acute Respiratory Infections in Children in Papua New Guinea. *Pediatr Res* 1983: 17: 1041-3.

55 Henehan J. Penicillin Gets Some Help Against Resistant Pathogens. *JAMA* 1982: 148(19): 2427.

56 Levy S, Burke JP, Wallace CK. Antibiotic Use and Antibiotic Resistance Worldwide. *Rev Inf Dis* 1987: 9(53): 5231-313.

57 Anonymous. *The Public Health Aspects of Antibiotics in Feedstuffs: Report on a Working Group*, Brenen, 1-5 October, 1973. Copenhagen, Denmark: WHO Regional Office for Europe. 1974.

58 Anonymous. Surveillance for the Prevention and Control of the Health Hazards Due to Antibiotic-Resistant Enterobacteria: Report of a WHO Meeting. 1978: *WHO Technical Report Series*, no. 624.

59 Anonymous. The Selection of Essential Drugs: Second Report of the WHO Expert Committee. 1979: *WHO Technical Report Series*, no 641.

60 Parker MT. Antibiotic Resistance in Pathogenic Bacteria. *WHO Chron.* 1982: 36(5): 191-6.

61 Philpott-Howard J, et al. Increase in Antibiotic Resistance in *H. influenzae* in the U.K. since 1977: Report of Study Group. *Br. Med. J. [Clin. Rsh]* 1982: 29: 284 (6329)/1597-9.

62 World Health Organization. The Rational Use of Drugs: Report of the Conference Experts, Nairobi, 25-29 November 1985. Geneva: *World Health Organization.* 1987.

63 Pan American Health Organization. Policies for the Production and Marketing of Essential Drugs. Washington, DC: PAHO. 1984: *Sci Pub* No. 462.

64 World Health Organization. Control of Antibiotic-resistant Bacteria: Memorandum Based on Report from WHO Meeting. 1983: *Bull. WHO* 61: 423-33.

65 Johansen KS, Storgaard M, Carstensen N, et al. An International Study on the Occurrance of Multiresistant Bacteria and Aminoglycoside Consumption Patterns. *Infection* 1988: 16: 313-22.

66 World Health Organization. Report of Scientific Group on the Control of Bacterial Resistance. Regional Office for the Western Pacific, Manila, Philippines: *WHO*, 1984.

67 Anonymous. The Bamako Initiative [Letter]. *Lancet* 1988: 2: 1366-7.

68 Mitsuhashi S. Drug Resistance in Bacteria. Tokyo: *Japan Scientific Societies Press*, 1982.

69 Amsterdam D. The Development of Resistance During Antimicrobial Therapy. Antimic. *News* 1989: 6(9): 72-3.

70 Galiardo E. Sensitivity of Bacteria from Infected Wounds to Penicillin II: Results in One Hundred and Twelve Cases. *War Med* 1945: 7: 100-3.

71 Finland M, Murray R, Harris HW, et al. Development of Streptomycin Resistance During Treatment. *JAMA* 1946: 132: 16-20.

[72] Colquhoun H, Weetch RS. Resistance to Chloramphenicol Developing During Treatment of Typhoid Fever. *Lancet* 1950: ii:621-623.

[73] Finland M, Wilcox C, Frank PF. *In vitro* susceptibility of human pathogenic strains of streptococci to seven antibiotics. *Amer J Clin Path* 1950: 20: 208-19.

[74] Finland M. Emergence of Antibiotic-resistant Bacteria. *N Engl J Med* 1955: 253(22): 969-78.

[75] Finland M. Emergence of Antibiotic-Resistant Bacteria. *N Engl J Med* 1955: 253(23): 1019-28.

[76] Finland M, et al. Development of Streptomycin Resistance During Treatment. *JAMA* 1946: 132: 16-21.

[77] Schiott CR, Stenderup A. Terramycin-, Aureomycin-, and Chloromycetin-dependent Bacteria Isolated from Patients. *Act Path et Microbiol Scandinav* 1954: 34: 410-6.

[78] Garrod LP, Shooter RA, Curwen MP. Results of Chemotherapy in Urinary Infections. *Brit Med J* 1954: 2: 1003-8.

[79] Womack CR. Terramycin Therapy of Urinary Tract Infections. *Arch Ing Med* 1952: 89: 240-57.

[80] Erlanson P, Jönsson G. Bacterial Aspects of Chemotherapy of Surgical Urinary Infections, Occurrence of Resistance to Chemotherapeutic Agents. *Acta Chir Scandinav* 1953: 106: 399-416.

[81] Jackson GG, Dallenbach FO, Kipnis GP. Pyelonephritis: Correlation of Clinical and Pathologic Observations in the Antibiotic Era. *M Clin North America* 1955: 39: 297-305.

[82] Lind HA, Suanton E, Trafton HM. Status of Bacterial Sensitivity Determinations with Relation to Single Antibiotic Therapy in Urinary Infections. *Antibiotics Annual, 1953-1954.* 1955: 542-7.

[83] Kass EH. Chemotherapeutic and Antibiotic Drugs in Management of Infections of the Urinary Tract. *Am J Med* 1955: 18: 764-781.

[84] Erwin C, Waisbren BA, Kruse R. Clinical and Laboratory Studies of Infections Due to *Pseudomonas aeruginosa* and *Pseudomonas species*. *Am J Med Sc* 1953: 266: 525-32.

[85] Bellamy WD, Klimer JW. Relation Between Induced Resistance to Penicillin and Oxygen Utilization. *J Bact* 1948: 55: 147-51.

[86] Price CW, Randall WA, Chandler VL, et al. Observations on *in vivo* and *in vitro*: Development of Bacterial Resistance to Streptomycin. *J Bact* 1947: 53: 481-488.

[87] Alexander HE, Leidy G. Mode of Action of Streptomycin on Type B *Hemophilus influenzae* II. Nature of Resistant Variants. *J Exper Med* 1947: 85: 607-21

[88] Seligmann E, Wasserman M. Induced Resistance to Streptomycin. *J Immunol* 1947: 57: 351-360.

[89] Rosanoff EI, Sevag MG. Alternate Metabolic Pathways in Streptomycin Sensitive and Resistant Strains of *Escherichia coli*. *Antibiotics and Chemother* 1953: 3: 495-504.

[90] Anderson K. Strain of Staphylococcus Resistant to Five Antibiotics. *J Clin Path* 1954: 7: 148-151.

[91] Hobson D. Activity of Erythromycin Against *Staphylococcus aureus*. *Brit Med J* 1954. 1: 236-239.

[92] Szybalski W. "Natural" and "Artificial" Penicillin Resistance in Staphylococci *(Micrococcus pyogenes var. aureus)*. *Antibiotics & Chemother* 1953: 3: 915-18.

[93] Chandler CA, Davidson VZ, Long PH, et al. Studies on Resistance of Staphylococci to Penicillin: Production of Penicillinase and its Inhibition by Action of Aureomycin. *Bull Johns Hopkins Hosp* 1951: 89: 81-89.

[94] McKee CM, Houck CL. Induced Resistance to Penicillin of Cultures of Staphylococci, Pneumococci and Streptococci. *Proc Soc Exper Biol & Med* 1943: 53: 33-5.

[95] Hsie JY, Bryson V. Genetic Studies on Development of Resistance to Neomycin and Dihydrostreptomycin in *Mycobacterium ranae*. *Am Rev Tuber* 1950: 62: 286-99.

[96] Pansy FE, Khan P, and Pagan JF, et al. Relationship Between Aureomycin, Chloramphnicol and Terramycin. *Proc Soc Exper Biol & Med* 1950: 75: 618-20.

[97] Fusillo MH, and Romansky MJ. Simultaneous Increase in Resistance of Bacteria to Aureomycin and Terramycin upon Exponsure to Either Antibiotic. *Antibiotics & Chemother* 1951: 1: 101-9.

[98] Eisman DC, Marsh WS, Mayer RL. Differentiation of Antibiotics by Resistant Strains. *Science* 1946: 103: 674-8.

[99] Rolfe RD, et al. Comparative *in vitro* Activity of New Beta-Lactam Antibiotics Against Anaerobic Bacteria. *Antimic Agtrs Chemother* 1981: 20(5): 600-9.

100 Gombert ME. Susceptibility of *Nocardia asteroides* to Various Antibiotics Including Newer ß-Lactams, Trimethoprim-Sulfa Methoxazole, Amikacin and NF Thienamycin. *Antimicrob. Agts. Chemoth* 1982: 21(5): 1011-12.

101 Fass RJ. Comparative *In Vitro* Activities of ß-Lactam-Tobramycin Combinations Against *Pseudomonas aeruginosa* and Multidrug-Resistant Gram-Negataive Enteric Bacilli. *Antimicrob Agts Chemother* 1982: 21(6): 1003-6.

102 Price SB, Flornoy DJ. Comparison of Antimicrobial Susceptibility Patterns Among Coagulase Negative Staphylococci. *Antimic Agts Chemother* 1982: 21(3): 436-40.

103 Davis TJ, Matsen JM. Prevalence and Characteristics of *Klebsiella species:* Relation to Association with a Hospital Environment. *J Infect Dis* 1974: 130: 402-5.

104 Mouton RP. Relationship Between Antibiotic Consumption and Frequency of Antibiotic Resistance of Four Pathogens -- a Seven-Year Survey. *J Antimicrob Chemother* 1976: 2(1): 9-19.

105 Washington JA 2nd. Microbial Resistance to ß-Lactam Antibiotics. *Mayo Clin Proc* 1982: 57(12): 781-3.

106 Fass RJ. Comparative *In-Vitro* Activities of 3rd Generation cephalosporins. *Arch Intern Med* 1983: 143(9): 1743-5.

107 Green MJ. The Emergence of Antimicrobial Resistance in New Zealand. *NZ Med J* 1979: 89(634): 314-6.

108 O'Brien TF, Acar JF, Medeiros AA, Norton RA, Goldstein F, Kent RL. International Comparison of Prevalence of Resistance to Antibiotics. *JAMA* 1978: 239(15): 1518-23.

109 Parker MT, Hewitt JH. Methicillin Resistance in Staphylococcus aureus. *Lancet* 1970: 1: 800-4.

110 Sparling PF. Antibiotic Resistance in Neisseria gonorrhoeae. *Med Clin North Am* 1972: 56: 1133-44.

111 Anderson ES. Transferable Drug Resistance in Salmonella in South and Central America. *Weekly Epidemiol Record* 1974: 8: 65-9.

112 Kirven LA, Thornsberry C. Transfer of Betalactamase Genes of *Neisseria gonnorrhoeae* by Conjugation. *Antimicrob Agents Chemother* 1977: 11: 1004-6.

[113] O'Brien TF, Kent RL, Medeiros AA: Computer-generated Plots of Results of Antimicrobial Susceptibility Tests. *JAMA* 1969; 210: 84-92.

[114] O'Brien TF, Kent RL, Medeiros AA. Computer Surveillance of Shifts in the Gross Patient Flora During Hospitalization. *J Infect Dis* 1975: 131: 88-96.

[115] Medeiros AA. Expanding Spectrum of antibiotic Resistance. *R I Med J* 1981: 64: 197-201.

[116] Levy SB. Microbial Resistance to Antibiotics. *Lancet* 1982: ii:83-8.

[117] Jacobs MR, Koornhof HJ, Robins-Browne RM, et al. Emergence of Multiply-resistant Pneumococci. *N Engl J Med* 1978: 299: 735-40.

[118] Spratt BG. Biochemical and Genetical Approaches to the Mechanism of Action of Penicillin. *Philos Trans R Soc Lond* [Biol] 1980: 289: 273-283.

[119] Neu HC. Changing Mechanisms of Bacterial Resistance. *Am J Med* 1984: 77 (1Part B): 11-23.

[120] Kahan FM, Kahan JS, Cassidy PJ, et al. The Mechanism of Action of Fosfomycin. *Ann NY Acad Sci* 1974: 235: 364-86.

[121] Levy SB. The Tetracyclines: Microbial Sensitivity and Resistance. in Grassi GG, Sabath, LD (eds). *New Trends in Antibiotics: Research and Therapy*, Amsterdam, Elsviere North Holland. 1981: 7-44.

[122] Shannon K, Phillips I. Mechanisms of Resistance to Aminoglycosides in Clinical Isolates. *J Antimicrob Chemother* 1982: 9: 91-102.

[123] Richmond MH, Sykes RB. The ß-Lactamases of Gram-negative Bacteria and their Role in Resistance to ß-Lactam Antibiotics. *Adv Microb Physiol* 1973: 9: 31-88.

[124] Garvey RJP, McMullin GP. Meningitis Due to ß-Lactamase Producing type B *Haemophilus influenzae* Resistant to Chloramphenicol. *Br Med J* 1983: 187: 1183-4.

[125] Tepper BS. Microbial Resistance to Drugs. in Bang BF, Sladen BK (eds): *The Biology of Populations*. New York, American Elsevier. 1969: 154-167.

[126] Gruneberg RN, Shaw EJ. The Influence of Antibiotic Treatment on Resistance Patterns of Coliform Bacilli in Childhood Urinary-Tract Infection. *J Med Microbiol* 1976: 9(2): 233-7.

[127] Takafuji, ET. The Effect of Antibiotic Drug Resistance on the Environment and its Impact on Public Health. *Prev Med* 1977: 6(2): 312-8.

128 Gardner P, Smith DH, Berr H, et al. Recovery of R-factors from a Drug Free Community. *Lancet* 1969: 2: 774-8,

129 Lepper MH, Moulton B, Dowling HF, et al. Epidemiology of Erythromycin Resistant Staphylococci in a Hospital Population: Effect on Therapeutic Activity of Erythromycin. *Antibiot Ann 1953* 1954: 308.

130 Mitsuhashi S. R-Factor Drug Resistance Plasmid, Blatimore MD: University Park Press, 1977.

131 Meyer DW, Lerman SJ. Rise and Fall of *Shigella* Antibiotic Resistance. *Antimicrob. Agents Chemother* 1980: 17: 101-2.

132 Palmer DL. Epidemiology of Antibiotic Resistance. *J Med* 1980: 11(4): 255-62.

133 Stamm WE, et al. Antimicrobial Prophylaxis of a Recurrent Urinary Tract Infections: A Double-Blind, Placebo-Controlled Trial. *Ann Int Med* 1980: 92: 770-5.

134 Hepler CD, Clyne KE, Donta ST. Rationales Expressed by Empiric Antibiotic Prescribers. *Am J Hosp Pharm* 1982: 39: 1647-55.

135 Price DJE, Sleigh JD. Control of Infection due to *Klebsiella aerogenes* in a Neurosurgical Unit by Withdrawal of all Antibiotics. *Lancet* 1970: 2: 1213-5.

136 Grimson RC, et al. A Statistical Test for Classification With Applications to the Characterization of Pathogens According to Antibiotic Susceptability Patterns. *Biometrics* 1981: 37(4): 753-61.

137 Holmberg SD, Solomon SL, Blake PA. Health and Economic Impacts of Antimicrobial Resistance. *Rev Inf Dis* 1987: 9(6): 1065-78.

138 Cohen S. Microbial Resistance to Antibiotic Agents. *Comp Ther* 1979: 5(5): 59-68.

139 Mitsuhashi S. Epidemiology and Genetics of R Factors. *Ann NY Acad Sci* 1972: 182: 141-52.

140 Fouace J. Mixed Cultures of *Staphylococcus aureus*: Some observations Concerning Transfer of Antibiotic Resistance. *Ann Microbiol* (Paris) 1981: 132 B(3): 375-86.

141 Jonklik WK, Willett HP, Amos DB, Zinsser H. *Microbiology*, New York, NY: Appleton-Century-Crofts, 1980: 271.

[142] Walia SK, Chugh TD,Sharma KB. Prevalence of R. Plasmid in *Klebsiella pneumoniae*. *Indian J Med Res* 1980: 71: 42-5.

[143] Clowes, R. Molecular Structure of Bacterial Plasmids. *Bacteriol Rev* 1972: 36: 361-405.

[144] Novick, RP. Penicillase Plasmids of *Staphylococcus aureus*. *Fed Proc* 1967: 26: 29-38.

[145] Wilson, R. The Clinical Application of Antibiotics 1952-1961. in Liebert J (ed) *Antibiotic Usage: The Medical Perspective* ; Sage Pub: 1963 : 877.

[146] Proc. of a Symposium held in Leternan Gen Hosp: *Changing Patterns of Bacterial Infection and Antibiotic Therapy*.San Francisco, CA, 1980

[147] Ounissi H, et al. Classification of Macrolide-Linclosamide-Streptogramine-B-Type Antibiotic Determinants. *Ann Microbiol* (Paris) 1981: 132B(3): 441-54.

[148] Caswell MW. R-Factor Mediated Gentamicin Resistance in "*Klebsiella Aerogenes*": A New Problem in Nosocomial Infection. *Quad Sclavo Diagn* 1979: (15) Suppl 1: 419-33.

[149] Anderson ES. The Molecula Relatedness of R-Factors in Enterobacteria of Human and Animal Origin. *J Gen Microbiol* 1975: 91(2): 376-82.

[150] Sadowski PL, Peterson BC, Gerding DN, Cleary PP. Physical Characterization of Two R Plasmids Obtained from an Outbreak of Nosocomial *Klebsiella pneumoniae* Infections. *Antimicrob Agts Chemother* 1979: 15: 618-24.

[151] Watanabe T. Evolutionary Relationship of R Factors with other Episomes and Plasmids. *Fed Proc Fed Am Soc. Exp Biol* 1967: 26: 23-8.

[152] Vescovo M, Morelli L, Botazzi V. Drug Resistance Plasmids in *Lact. acidophilus* and *Lact. reuteri*. *Appl Environ Microbiol* 1982: 43(1): 50-6.

[153] Moorehouse EC. Transferable Drug Resistance in Enterobacteria Isolated from Urban Infants. *Br Med J* 1969: 2: 405-7.

[154] Linton KB, Richmond MH, Bevan R, et al. Antibiotic Resistance and R Factors in Coliform Bacilli isolated from Hospital and Domestic Sewage. *J Med Microbiol* 1974: 7: 91-103.

[155] Isenberg HD, Berkman JI. The Role of Drug-Resistant and Drug-Selected Bacteria in Nosocomial Disease. *Ann NY Acad Sci* 1971: 182: 52-8.

156 Lacey RW. Do Sulphonamide-Trimethoprim Combinations Select Less Resistance To Trimethoprim Than The Use Of Trimethoprim Alone? *J Med Microbiol* 1982: 15(4): 403-27.

157 Hoeprich PD. Induction of Resistance in *Staphylococcus aureus* and *Klebsiella pneumoniae* by Exposure to Cephalothin and Cefoxitin. *J Infect Dis* 1976: 133(6): 681-5.

158 Toala P, McDonald A, Wilcox C, et al. Susceptibility of group D *Streptococcus (Enterococcus)* to 21 Antibiotics *in vitro*, with special reference to species differences. *Am J Med Sci* 1969: 258: 416-30.

159 Brandberg A, Lindblom GB, Franzen C. The Resistance of 150 *Klebsiella* and *E.coli* strains isolated from patients Suffering from Bacteriaemia. *Scand J. Infect Dis* (suppl) 1976: (8): 103-5.

160 Palomares JC,Perea EJ. Comparison Between Plasmids of *Salmonella* and Other Enterobacteria Isolated from the Same patients. *Ann Microbiol* (Paris) 1982: 133(2): 301-310.

161 Lyons RW, Samples CL,DeSilva HN, et al. An Epidemic of Resistant *Salmonella* in a Nursery. Animal to Human Spread. *JAMA* 1980: 243: 546-7.

162 Jorgensen ST. Relatedness of Chloramphenicol Resistance Plasmids in Epidemiologically Unrelated Strains of pathogenic *Escherichia coli* from Man and Animals. J Med Microbiol 1983: 16(2): 165-73.

163 Johnston NA, Kolator B. Emergence in Britain of ß-Lactamase-Producing Gonococci with New Plasmid Combination. *Lancet* 1982: 1: 445-6.

164 Richard SH. Plasmids and Transposons Acquired by *Salmonella typhi* in Man. *Plasmid* 1982: 8(1): 9-14.

165 Casewell MW. Gentamicin-Resistant *Klebsiella aerogenes* as a Clinically - Significant source of Transferrable Antibiotic Resistance. *J Antimicrob Chemother* 1981: 8(2): 153-60.

166 LeBougnenec L, et al. Conjugative R Plasmids in S&P faecium (GPD). *Antimicrob Agts Chemother* 1982: 21(5): 698-705.

167 Mays TD, Smith CJ, Welch RA, Delfini C, Macrina FL. Novel Antibiotic Resistance Tranfer in Bacteroides. *Antimic Agts Chemother* 1982: 21(1): 110-118.

168 Brefort GM, Magot M, Ionesco H, et al. Characterization and Transfer Ability of *Clostridium perfringens* Plasmids. *Plasmid* 1977: 1: 52-66.

169 Privitera G, Dublanchet A, Sebald M. Transfer of Multiple Antibiotic Resistance Between Subspecies of *Bacteroides fragilis*. *J Infect Dis* 1979: 139: 83-87.

170 Tally FP, Snydman DR, Gorbach SL, et al. Plasmid Mediated, Transferable Resistance to Clindamycin and Erythromycin in *Bacteroides fragilis*. *J Infect Dis* 1979: 139: 89-92.

171 Malamy MH, Tally FP. Gene Transfer Between *Bacteroides Fragilis* and *Escherichia Coli*. *Alliance Prudent Use Antibiot News* 1986: 4(1): 1-7.

172 Goldstein FW, Acar JF. Evolution of Multi-Resistance in *Vibrio cholerae*. *APUA News* 1985: 3(2): 1-6.

173 Courtney MA, Miller JR, Summersgill J, Melo J, Raff MJ, Streips UN. R-Factor Responsible for an Outbreak of Multiply Antibiotic-Resistant *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 1980: 18(6): 926-9.

174 Lowbury EJL, Ayliff GAJ. *Drug Resistance in Antimicrobial Therapy*. Springfield IL: Charles C. Thomas, Pub. 1974.

175 Mollering RC. ß-Lactamase - Producing Enterococci: A New Challenge for Microbiologists and Clinicians. *APUA News* 1991: 9(2): 1-3.

176 Sabath LD. Mechanisms of Resistance to ß-Lactam Antibiotics in Strains of *Straphylococcus aureus*. *Ann Int Med* 1982: 97(3): 339-41.

177 Zervos, MJ, Dembinski S, Mikesell T, et al. High-Level Resistance to Gentamicin in *Streptococcus faecalis:* Risk Factors and Evidence for Exogenous Acquisition of Infection. *J Infect Dis* 1986: 153(6): 1075-83.

178 Catron D. Appraisal of Results of Feeding Antibiotics to Swine. *Agric & Food Chem* 1953: 1: 1100-12.

179 DuPont HL, Steele JH. Use of Antimicrobial Agents in Animal Feeds: Implications for Human Health. *Rev Inf Dis* 1987: 9(3): 447-60.

180 Marshall E. Antibiotics in the barnyard. *Science* 1980: 208: 376-9.

181 Antibiotics in Animal Feeds. *Report No. 88, Council for Agricultural Science & Technology*, Ames Iowa 1981; 1-79.

182 Levy SB, Fitzgerald GB, Macone AB. Changes in Intestinal Flora of Farm Personnel After Introduction of a Tetracycline Supplemented Feed on a Farm. *N Engl J Med* 1976: 295: 503-8.

183 Jones AM. *Escherichia coli* in Retail Samples of Milk and Their Resistance to Antibiotics. *Lancet* 1971: 2: 347-9.

184 Moorhouse EC, O'Grady MF, O'Conner H. Isolation from Sausages of Antibiotic-resistant *Escherichia coli* with R Factors. *Lancet* 1969: 2: 50-7.

185 Shooter RA, Cooke EM O'Farrell S, et al. The Isolation of *Escherichia coli* from a Poultry Packing Station and an Abbattoir. J Hyg (Camb.) 1974: 73: 245-7.

186 Walton JR, Lewis LE. Contamination of Fresh and Cooked Meats by Antibiotic-resistant Coliform Bacteria. *Lancet* 1971: 2: 255-7.

187 Beam TR. A Critical Appraisal of the Role of Animal Models of Infection for Assessing Antimicrobial Activity. *Antimic Newslett* 1984: 1(9): 67-73.

188 Linton AH, Howe K, Bennett PM, et al. The Colonization of the Human Gut by Antibiotic Resistant *Escherichia coli* from Chickens. *J Appl Bact* 1977: 43: 465-9.

189 Levy SB, Fitzgerald GB, Mancone AB. Spread of Antibiotic-resistant Plasmids from Chicken to Chicken and from Chicken to Man. *Nature* 1976: 260: 40-2.

190 O'Brien TF, Hopkins JD, Gilleece ES, et al. Molecular Epidemiology of Antibiotic Resistance in Salmonella from Animals and Human Beings in the United States. *N Engl J Med* 1982: 307: 1-6.

191 Holmberg SD. Drug-Resistant *Salmonella* species from Animals Fed Antimicrobics. *Infec Dis News* 1988: 5(4): 25-8.

192 Jukes TH. Public Health Significance of Feeding Low Levels of Antibiotics to Animals. *Adv Appl Microbiol* 1973: 16: 1-30.

193 Anonymous. Why has Swann failed? (Editorial) *Br Med J* 1980: 280: 1195-6.

194 National Research Council to Study the Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds. The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Foods. *Nat Acad Sci* Washington D.C.

195 Swann, MM. Report: Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine. CMDN 4190 London, HMSO, 1969.

196 Threlfall BJ, Ward LR, Rowe B. Spread of Multiresistant Strains of *Salmonella typhimurium* phage types 204 and 193 in Britain. *Br Med J* 1978: ii: 997.

197 Richmond MH, Linton KB. The use of Tetracycline in the Community and its Possible Relation to the Excretion of Tetracycline-resistant Bacteria. *J Antimicrob Chemother* 1980: 6: 31-41.

198 Martinez-Mández JL, Baquero F. Genetic Linkage of Antibiotic Resistance and Bacterial Virulence. *APUA News* 1988: 6(3): 1-3.

199 Stolar MHJ. Drug Use Review: Operational Definitions. *Am J Hosp Pharm* 1978: 35: 76-8.

200 Laaberki-Jeanjean MF, et al: Antibiotic Therapy and Hospital Practice. *Maroc Med* 1981: 3(1): 487-99.

201 Braude AI (Ed). Antimicrobial Drug Therapy: Major Problems in Internal Medicine. Philadelphia: Saunders 1976: Vol. 8.

202 Kucers A, Bennett N McK. *The Use of Antibiotics: A Comprehensive Review with Clinical Emphasis.* 3d edition, 1979.

203 Louria DB, Kaminski T: The Effect of Four Antimicrobial Drug Regimens on Sputum Superinfection in Hospitalized Patients. *Am Rev Respiratory Dis* 1962: 85: 649-65.

204 Selden R, Lee S, Wang WLL, et al. Nosocomial *Klebsiella* infections: Intestinal Colonization as a Reservoir. *Ann Int Med* 1971: 74: 657-64.

205 Pollack M, Charache P, Nieman RE, et al. Factors influencing colonization and Antibiotic Resistance Patterns of Gram-negative Bacteria in Hospital Patients. *Lancet* 1972: ii: 668-71.

206 Holzman RS, Florman AL, Podrid PhH, et al. Drug-associated Diarrhoea as a Potential Reservoir for Hospital Infection. *Lancet* 1974: i: 1195-1198.

207 Hirsch DC, Burton GC, Blenden DC. The Effect of Tetracycline Upon Establishment of Escherichia coli of Bovine Origin in the Enteric Tract of Man. *J Applied Bact* 1974: 37: 327-33.

208 VanderWaaij D, Berghuis-DeVries JM, Lekkerkerk-VanderWees JEC. Colonization Resistance of the Digestive Tract in conventional and Antibiotic-treated Mice. *J Hyg* 1971: 69: 405-11.

209 Wieggersma N, Jansen G, VanDerWaaij D. Effect of 12 Antimicrobial Drugs on the Colonization Resistance of the Digestive Tract of Mice and on Endogenous Potentially Pathogenic Bacteria. *J Hyg* 1982: 88(2): 221-30.

210 Finland M. Changes in Susceptibility of Selected Pathogenic Bacteria to Widely Used Antibiotics. Ann NY Acad Sci 1971: 182: 5-20.

211 Finland M. Changing prevalence of Pathogenic Bacteria in Relation to Time and the Introduction and Use of New Antimicrobial Agents. in Finland M, Marget W, Bartmann K (ed) Bacterial Infections Bayer-Symposium III, Grosse Ledder, Germany Oct 23-27, 1970. Springer -Verlag 1971.

212 Finland M, Haight TH. Antibiotic Resistance of Pathogenic Staphylococci; Study of Five Hundred Strains Isolated at Boston City Hospital from October 1951 to February 1952. *Arch Intern Med* 1953: 91: 1453-58.

213 Finland M, Jones WF, Bennett IL. Antibiotic Susceptibility and Phagetypes of Pathogenic Staphylococci. A Study of Two Hundred Ten Strains Isolated at Boston City Hospital in 1955. *Arch Intern Med* 1959: 104: 365-77.

214 Finland M, Hirsch HA,Wallmark G. Pathogenic Staphylococci Isolated at Boston City Hospital in 1958. *Arch Intern Med* 1960: 105: 383-97.

215 Kjellander JO, Klein JO, Finland M. *In vitro* Activity of Penicillin Against *Staphylococcus albus*. *Proc Soc Exp Biol Med* 1963: 113: 1023-31.

216 Steigbigel NH, Reed CW, Finland M. Susceptibility of Common Pathogenic Bacteria to Seven Tetracycline Antibiotics *in vitro*. *Am J Med Sci* 1968: 255: 179-95.

217 Hermans PE. General Principles of Antimicrobial Therapy. *Mayo Clinic Proc* 1977: 52: 603-10.

218 Stolar MH. Conceptual Framework for Drug Usage Review, Medical Audit and Other Patient Care Review Procedures. *Am J Hosp Pharm* 1977: 34: 139-40.

219 Castle M, Wilfert CM, Cate TR, et al: Antibiotic Use at Duke University Medical Center. *JAMA* 1977: 237: 2819-22.

220 Shaffnew W, Ray WA, Federspiel CF. Surveillance of Antibiotic Prescribing in Office Practice. *Ann Intern Med* 1978: 89: 796-9.

221 D'Achille KM, Flickinger DB, Riethmiller MK, Facey WK. Antimicrobial Use Review in a Family Practice Setting. *Am J Hosp Pharm* 1981: 38: 696-9.

222 Clarke JT. Planning Antibiotic Therapy of Pneumonia. *Geriatrics* 1977: 32: 51-9.

223 Hobb GL, Meyer K, Chaffee E. Observations on the Mechanism of Action of Penicillin. *Proc Soc Exp Biol Med* 1942: 50: 281-5.

224 Tomasz A, Albino A, Zanati E. Multiple Antibiotic Resistance in a Bacterium with Suppressed Autolytic System. *Nature* 1970: 227: 138-40.

225 Amsterdam D. Assessing Cidal Activity of Antimicrobial Agents: Problems and Pitfalls. *Antimicrob News* 1990: 7(7): 49-56.

226 Yu VL, Fagan LM, Wraith SM, Clancey WJ, Scott C, Hannigan J, Blum RL, Buchanan BG, Cohen SN. Antimicrobial Selection by a computer: A Blinded Evaluation by Infectious Diseases Experts. *JAMA* 1979: 242(12): 1279-82.

227 InterQual. Antibiotic Use Review and Infection Control: Evaluating Drug Use Through Patient Care Audit. Chicago IL:1979.

228 Reed DM, et al. Antimicrobial Use Review in Ambulatory Care Using Computer-Assisted Medical Record Audit. *Am J Hosp Pharm* 1982: 39(2): 280-4.

229 Moller JK, Bak AL, Bulow P, Christiansen C, Christiansen G, Seenderup A. Transferable and Non-Transferable Drug Resistance in Enteric Bacteria from Hospital and from General Practice. *Scand J Infect Dis* 1976: 8(2): 112-6.

230 Pritazsky V, Koskova L, Kremenova AZ, Krcmery V. R-Plasmide in Enterobacteriacerae From the Hospital Environment: *Zentralbl-Bakteriol* 1978: 242(2): 216-21.

231 Kass EH, Evans DA. "Introduction" to Vol. 1, No. L. Future Prospects and Past Problems in Antimicrobial Therapy: The Role of Cefoxitin: *Rev Inf Dis* 1979: 1(1) 2-3.

232 Sanders CC. Novel Resistance Selected by the New Expanded-Spectrum cephalosporins: A Concern: *J Inf Dis* 1983: 147(3): 585-9.

233 Gootz TD, Sanders CC, Goering RV, et al. Resistance to Cefamandole: Depression of ß-lactamases by Cefoxitin and Mutation in *Enterobacter cloacae*. *J Infect Dis* 1982: 146: 34-42.

234 Lampe MF, Allan BJ, Minshenba, et al. Mutational Enzymatic Resistance of *Enterobacter species* to ß-lactam Antibiotics. *Antimicrob Agents Chemother* 1982: 21: 655-660.

235 Mangi RJ, Kundargi RS, Quintinni R, et al. Development of Meningitis During Cephalothin Therapy. *Ann Intern Med* 1973: 78: 347-51.

236 Findell CM, Sherris JC. Susceptibility of *Enterobacter* to Cefamandole: Evidence for a high mutation rate to resistance. *Antimicrob Agents Chemother* 1976: 9: 970-4.

237 Jones RN. The Antimicrobial Susceptibility Test: Rapid and Overnight, Agar and Broth, Automated and Conventional, Interpretation and Trend Analysis. in V Lorian [ed.] Significance of Medical Microbiology in the Care of Patients, 2nd Ed. BaltimoreMD: Williams and Wilkins, 1982: 341-69.

238 Whiteside M, Moore J, Ratzan K. An Investigation of Enterococcal Bacteremia. *Am J Infect Control* 1983: 11: 125-9.

239 McGowan TEJr, Barnes MW, Finland M. Bacteremia at Boston City Hospital: Occurrence and Mortality During 12 Selected Years (1935-1972) with Special Reference to Hospital-Acquired Cases. *J Infect Dis* 1975: 132 :316-35.

240 Spengler RF, Greenough WBIII, Stolley PD. A Descriptive Study of Nosocomial Bacteremias at the Johns Hopkins Hospital, 1968-1974. *Johns Hopkins Med J* 1978: 142: 77-84.

241 Maki DA. Nosocomial Bacteremia: An Epidemiologic Overview. *Am J Med* 1981: 70: 719-32.

242 Centers for Disease Control. National Nosocomial Infection Study Reports, Atlanta, 1983.

243 Homayouni H, Gross PA, Setia U, et al. Leukopenia Due to Penicillin and cephalosporin Homologues. *Arch Internal Med* 1979: 139: 827-8.

244 Murray BE, Mederski-Samoraj B: Beta - Lactamase Resistant *Enterococcus faecalis*. *J Clin Invest* 1983: 72: 1168-71.

245 Murray BE, Church DA, Wagner N, et al. *Antimicrob Agents Chemother* 1986: 30: 861-4.

246 Liss RH, Bachelor FR. Economic Evaluations of Antibiotic Use and Resistance - A Perspective: Report of Task Force 6. *Rev Infect Dis* 1987: 9(53): S297-312.

247 Kunin CM, Johansen KS, Worning AM, et al. Report of a Symposium on Use and Abuse of Antibiotics Worldwide. *Rev Inf Dis* 1990: 12(1): 12-19.

248 Holloway WJ. The Problem of Antibiotic Overdose. *Del Med J* 1982: 54(4): 211-2.

249 Alves Survey. Cited in *Global Survey of the Pharmaceutical Industry*, UNIDO, ID/WG 331-6, 1980.

250 Pharmaceutical Preparations, Except Biologicals, Current Industrial Reports. US Dept of Commerce, Bureau of the Census, Washington, DC, 1982.

251 Murry BE, Mederski-Samoraj B, Foster SK, et al. *In Vitro* Studies of Plasmid-Mediated Penicillinase from *Streptococcus faecalis* suggest a Staphylococcal Origin. *J Clin Invest* 1986: 77(1): 289-93.

252 Geddes AM. Good Antimicrobial Prescribing: Introduction: *The Lancet* 1982: ii: 82.

253 Jones WF, Finland M. Susceptability of *Enterococci* to Eleven Antibiotics *in vitro*. *Am J Clin Path* 1984: 27: 467-81.

254 Chen HY, Williams JD. Penicillin-binding Proteins in *Streptococcus faecalis and S. faecium*. *J Med Microbiol* 1987: 23(2): 141-7.

255 Kaye D. *Enterococci*. Biologic and Epidemiologic Characteristics and *in vitro* susceptibility. *Arch Inter Med* 1982: 142(11): 2006-9.

256 Toda M, Arao N, Nohara C, et al. In vitro studies on the Antibacterial Activities of YM-13115, a new broad-spectrum cephalosporin. *Antimicrob Agents Chemother* 1985: 27(4): 565-9.

257 Goldstein EJ, Citron DM. Comparative in vitro inhibitory and killing activity of Cefpirome, ceftazidine and cefotaxime against pseudomonas aeruginosa, enterococci, Staphylococcus epidermidis, and methicillin - Susceptible and - resistant and tolerant and nontolerant Staphylococcus aureus. *Antimicrob Agents Chemother* 1985; 28(1): 160-2.

258 Finland M, Garner C, Wilcox C, et al. Susceptibility of "enterobacteria" to penicillins, cehalosporins, lincomycins, erythromycin, and rifampin. *J Infect Dis* 1976: 134(suppl.): 575-596.

259 Murray BE. The life and times of the *Enterococcoccus*. *Clin Microbiol Rev* 1990: 3: 46-65.

260 Mollering RC Jr, Weinberg AN. Studies on Antibiotic Synergism Against Enterococci: *J Clin Invest* 1971: 50: 2580-4.

261 Wilkowske CJ, Facklam RR, Washington JA II, et al. Antibiotic Synergism: Enhanced Susceptibility of Group D Streptococci to Certain Antibiotic Combinations. *Antimicrob Agents Chemother* 1970: 10: 195-200.

262 Louie M, Simor AE, Szerto S, et al. Susceptibility Testing of Clinical Isolates of *Enterococcus faecium* and *Enterococcus faecalis*. *J Clin Micro* 1992: 30(1): 41-45.

263 Shlaes D, Levy S, Archer G. NIH Workshop on Antibiotic Resistance. *National Institute of Allergy and Infectious Disease (NIAID)* Annapolis MD, Oct 1990.

264 Spencer RC, Philip JR. Effect of Previous Antimicrobial Therapy on Bacterial Findings in Patients with Primary Pneumonia. *Lancet* 1973: 2: 349-50.

265 Finland M. Emergence of Resistant Strains in Chronic Intake of Antibiotics: A Review: Proc. First Int. Conference on Antibiotics in Agriculture. Nat Ac Sci/Nat Reh Cl. Pub No. 397: 233-58, Washington, 1956.

266 Böttcher H. *Wonder Drugs: A History of Antibiotics*, Lippincott, 1964.

267 Williams REO. Controlling Antibiotic Resistance Without Eschewing Antibiotics: in The Control of Antibiotic-Resistant Bacteria (ed)Stuart-Harris Sir CH, Harris DM. Academic Press, London, 1982.

268 Col NF, O'Connor RW. Estimating Worldwide Current Antibiotic Usage: Report of Task Force 1. *Rev Infect Dis* 1987: 9(53): S232-43.

269 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1974. USITC Pub. 776, Washington DC 1976.

270 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1980. USITC Pub. 1173, Washington DC 1981.

271 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1983. USITC Pub. 1.14 983, Washington DC 1984.

272 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1983. USITC Pub. 984, Washington DC 1985.

273 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1985. USITC Pub. 1409, Washington DC 1986.

274 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1986. USITC Pub. 1.14 983, Washington DC 1984.

275 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1983. USITC Pub., Washington DC 1987.

276 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1974. USITC Pub. 776, Washington DC 1976.

277 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1985. USITC Pub. 1409, Washington DC 1986.

278 United States International Trade Commission. Synthetic Organic Chemicals: United States Production and Sales, 1984. USITC Pub. 984, Washington DC 1985.

279 Nesbitt, E. Drug Utilization in the United States: 1988. Tenth Annual Review. US Department of Commerce National Technical Information Service, ITC 1(14): 988.

280 Baum CB, Kennedy DL, Knapp DE, et al. Drug Utilization in the US - 1984: Sixth Annual Review. US Department of Commerce National Technical Information Service, ITC FDA/CDB, 86-122, 1985.

281 Baum CB, Kennedy DL, Knapp DE, et al. Drug Utilization in the US - 1985: Seventh Annual Review. US Department of Commerce National Technical Information Service. International Trade FDA/CDB-87/24, 1986.

282 Baum CB, Kennedy DL, Knapp DE, et al. Drug Utilization in the US - 1986: Eighth Annual Review. US Department of Commerce National Technical Information Service. International Trade FDA/CDB-88/18, 1987.

283 Tomita D, Baum C, Kennedy DE, et al. Drug Utilization in the US - 1987: Ninth Annual Review. US Department of Commerce National Technical Information Service. International Trade FDA/CDER-89/20, 1988.

284 Tomita DK, Kennedy DL, Baum C, et al. Drug Utilization in the US - 1988: Tenth Annual Review. US Department of Commerce National Technical Information Service. International Trade FDA/CDER-90/9, 1989.

285 Kennedy DL, Baum CS, Forbes MB, et al. Drug Utilization in the US - 1980 Second Annual Review. Drug Use Analysis Branch Food and Drug Administration, Rockville, MD: FDA, 1981.

286 Atkinson BA, Lorian V. Antimicrobial Agent Susceptibility Patterns of Bacteria in Hospitals from 1971 to 1982. *J Clin Micro* 1984: 20(4): 796-6.

287 Baum C, Kennedy DL, Forbes MB, et al. Drug Utilization in the US - 1981 Third Annual Review. Drug Use Analysis Branch Food and Drug Administration, Rockville, MD: FDA, 1981.

288 Baum C, Kennedy DL, Knapp ED, et al. Drug Utilization in the US - 1985 Seventh Annual Review. Drug Use Analysis Branch Food and Drug Administration, Rockville, MD: FDA, 1986.

289 Bureau of the Census. Estimates of the Population of the United States to April 1, 1985. Population Estimates and Projections, Series P-25. No. 969, 1985.

James T. Griffith

134 Hathaway Road
North Dartmouth, Massachusetts 02747-2715

Education:

1970	**B.S.** in Medical Technology *University of Massachusetts* Dartmouth
1970	M.T. (ASCP) The Memorial Hospital of Rhode Island, Pawtucket, RI
1976	**M.S.** in Medical Laboratory Science *University of Massachusetts* Dartmouth
1978 - present	**CLS** National Certification Agency for Medical Laboratory Personnel
1984 - present	**Ph.D.** (Clinical Microbiology) graduate work Walden University, Minneapolis, Minnesota

Employment:

1970 - 1972	Union Hospital, Fall River, Massachusetts Staff Technologist promoted to Chief Microbiologist Coordinator of Laboratory Lecture Series
1972 - 1974	Bristol Community College, Fall River, Massachusetts Assistant Professor
1972	Coordinator of the Medical Laboratory Technician Program
1973	Director of the Medical Laboratory Technician Program
1974 - present	*University of Massachusetts* Dartmouth (formerly Southeastern Massachusetts University) North Dartmouth, Massachusetts
1974 - 1976	Instructor of Medical Laboratory Science
1976 - 1978	Assistant Professor of Medical Laboratory Science
1978 - 1984	Associate Professor of Medical Laboratory Science
1984 - present	Professor of Medical Laboratory Science
1985 - present	Chairperson of Department

Professional Activities:

Member

American Society for Medical Technology
American Society for Microbiology
Massachusetts Association for Medical Technology
Southeastern New England Society for Medical Technology
Rhode Island Society for Microbiology
Southeastern Massachusetts Health Planning and Development, Inc.
Pan American Group for Rapid Viral Diagnosis
Sigma Xi -Science Research Society - *U Mass* Dartmouth Club

James T. Griffith

Director	Southeastern New England Clinical Microbiology Research Group
Director	Corsair MicroGraphics Project

American Society for Medical Technology (ASMT)

1969 - 1970	Member, Student Board of Directors
1971	District Census Chairman, National Laboratory Census, National Centers for Disease Control
1974 - 1977	Region I Secretary/Treasurer
1974 - 1978	Delegate from Massachusetts to the ASMT House of Delegates
1975 - 1978	Member, Government Liaison Committee
	Keyman Program Sen. Edward M. Kennedy (1975-1976)
	Sen. Edward W. Brooke (1976- 1978)
1978 - 1979	Chairman, National Health Planning Committee
1980	Contributing Member, (Mycoplasma) Virology/Chlamydia Subcommittee of the Microbiology section of the Scientific Assembly
1983	Chairman, Region I Government Affairs Committee
1985 - 1986	Reviewer, ASMT Performance Objectives Task Force, Bacteriology
1987 - 1988	Member, Editorial Review Board of *Clinical Laboratory Science*
	Presidential Task Force on AIDS
	Advisor, Campbell Communications AIDS Education Project - Nominated by the Microbiology Section of the ASMT Scientific Assembly
1988 - present	Editor, Newsletter of the Microbiology Section, Scientific Assembly, American Society for Medical Technology
1988 - 1989	Consulting Editor, *Clinical Laboratory Science*
1988 - 1990	Chairperson, ASMT Multicompetent Health Practitioner Task Force
1989 - 1990	Reviewer, Joseph Kleiner Memorial Award, ASMT Education & Research Fund, Inc.
1988 - present	Member, ASMT Government Affairs Committee
	Member, Region I Council
1989 - 1991	Member, Awards Committee, Microbiology Section of the Scientific Assembly

Massachusetts Association for Medical Technology (MAMT)

1969 - 1970	Student Treasurer
	Member, Student Board of Directors
1970 - 1971	Liaison to Student Organization
1971 - 1972	State Advisory Council
1972	Coordinator Student Session, MAMT Annual Meeting, Boston, MA
1972 - 1973	Treasurer
1972 - 1974	Member, Constitution and Bylaws Committee
1974 - 1977	Member, Education Committee
1975 - 1977	Chair, Education Committee
1975 - 1977	Chair, Task Force on Career Awareness
	Microbiology Section Representative to the MAMT Scientific Assembly
1976	Chair, President's Task Force on Membership Development
1976 - 1977	Special Liaison from the Board of Directors to the MAMT Scholarship Fund, Inc. Awards Committee
1977 - 1979	Co-Chair, Standards and Criteria Task Force
1977 - 1980	Member, Board of Directors
1982 - 1984	Chair, Government Liaison Committee
1987 - 1990	Chairperson, Government Affairs Committee

	Member, Long Range Planning Committee
1989 - 1990	President-Elect
1990 - 1991	President

Southeastern New England Society for Medical Technology (SNESMT)

1971	Founding member
1971 - 1973	President
1973 - 1974	Chair, Membership Development Committee
1974 - 1976	Chair, Scientific Assembly
1975 - 1976	Chair, Southeastern Massachusetts Task Force on Medical Technology Career Awareness
1987 - 1990	President
1987 - 1992	Chair, Rhode Island Licensure Group

National Certification Agency for Medical Laboratory Personnel (NCA)

1979 - present	Item writer for Microbiology section of baccalaureate degree, associate degree and specialty examinations
1989 - 1992	Member (Microbiology representative), Exam Council

Southeastern Massachusetts Health Planning and Development, Inc. (SMHPD)

1976 - 1979	Member, Board of Directors Representative for the Allied Health Professions
1976 - 1979	Vice-Chairman, Project Review Committee
1977	Chair, Project Review Committee
	Member, Reorganization Task Force
	SMHPD Representative to the Massachusetts Office of State Planning: State and Regional Comprehensive Health Planning Task Force on Standards and Criteria
1978	Chair, Project Review Manual Task Force
1979	Consultant on National Health Insurance
1980 - 1983	Member, Ambulatory Care Committee

Pan American Group for Rapid Viral Diagnosis

1980 - 1981	Member, Issues Committee

Special Appointments:

1976 - 1977	Massachusetts Department of Public Health 5 Year Health Plan Development Task Force
1976 - 1980	Special Consultant to the Southeastern Massachusetts Allied Health Council on Health Issues and Legislation
1977 - 1978	Office of State Health Planning Task Force on Laboratory Standards and Criteria
1978	Member, Legislative Committee, Massachusetts Health Council
1979 - 1982	Massachusetts Department of Public Health Advisory Committee on Clinical Laboratories

James T. Griffith

Corsair MicroGraphics Project

1986 - 1991 Director, Clinical Laboratory Science Software design and distribution

Sigma Xi - *University of Massachusetts* Dartmouth Club

1985 Elected to membership in Sigma Xi - *UMass* Dartmouth Club
1991 President - elect, - *UMass* Dartmouth Club
1992 President, - *UMass* Dartmouth Club

Consultantships:

1972 - present Consultant in Clinical Microbiology
Charlton Memorial Hospital
Fall River, Massachusetts

1974 - 1976 Consultant in Clinical Microbiology
The Miriam Hospital
Providence, Rhode Island

1974 - present Consultant in Education, MLT Program
Bristol Community College Fall River, Massachusetts

1976 - 1979 Special Consultant: Health Issues and Legislation
Southeastern Massachusetts Allied Health Council

1976 - present Consultant in Clinical Microbiology
Veterans' Administration Hospital Brockton, Massachusetts

1978 - 1979 Consultant to the Division of Personnel Administration
Commonwealth of Massachusetts

Reviewer: Manuscript *Microbiology for the Health Sciences*, Duxbury Press

1980 - 1990 Special Consultant to the President, MAMT issues of health care legislation

Grants:

1976 S.M.U. Foundation Grant
monograph "A Medical Technologist's Guide to Health Care Legislation"

1981 - 1983 Southeastern Massachusetts Area Health Education (AHEC) federal grant
Lecturer in Continuing Education:
*Medical Parasitology
*Advanced Medical Parasitology
*Clinical Mycology
*Antimicrobial Agents
*Basic Clinical Virology

James T. Griffith

Papers Published:

1979	HSA's - Where do we go from here? **ASMT NEWS** January
	Valliere W & Griffith JT: Endocarditis caused by *Mycobacterium tuberculosis* and *Mycobacterium fortuitum:* A Case Study. **Am J Med Tech**, January.
	Griffith JT: *Health Planning*. **Am J Med Tech**, February.
1986	Griffith JT: *The Virology of AIDS: Taxonomy, Molecular Biology, and Pathogenicity.* **Am J Med Tech** 3(3):149-51.
1987	Griffith JT: *Antimicrobial Database* for use with Macintosh computers - shareware offered through **Apple Computer Co. Database**
1992	Griffith JT: *OSHA Regulations for Occupational Exposure to Bloodborne Pathogens*. in: Rosenberg SA, ed. **Physician Laboratory Regulations Manual.** Washington DC: Thompson Publishing Group.

Honors and Awards:

1975	Biographee, Marquis' **Who's Who in the East**
1976	MAMT Board Award - for "outstanding leadership and contributions to the profession of medical technology"
	MSAMT Board Award - for "guidance and contributions to students"
1977	ASMT Omicron Sigma Award for "outstanding service"
	MAMT Member of the Year
	MSAMT Board Award
1978	ASMT Omicron Sigma Award
1983	ASMT Omicron Sigma Award
1988	Sherwood/ASMT Professional Achievement Award in Microbiology
	Board Award, Mass Association for Medical Technology for service to MAMT
	ASMT Omicron Sigma Award
1989	ASMT Omicron Sigma Award
	Member of the Year, MAMT
1990	Robin H. Mendelson Memorial Award for Outstanding Contributions to the Profession of Medical Technology (development of the ASMT Consensus Project)
1991	ASMT Member of the Year
1992	Elected member, Alpha Mu Tau, the national honor fraternity of medical laboratory science
	ASMT Board of Directors Award (to the Department of Medical Laboratory Science) for their work on the CLIA'88 response

Papers Presented:

1974	Panelist, Medical Technology Education MAMT Annual Meeting
	What is Mycology? MAMT Annual Meeting

James T. Griffith

1975
Ultrastructure as a Component of Viral Taxonomy
Anna Maria College, Paxton, Massachusetts
Quality Control in Microbiology part of a special series:
Quality Control in the Clinical Laboratory
Rhode Island Health Science Council
Report on Health Legislation Developments: The Emergence of Health Systems Agencies
MAMT Annual Meeting

1976
Clinical Laboratory Improvement Act: Update
MAMT Annual Meeting
Panelist: Impact of Federal Regulation
MAMT Semi-Annual Meeting
Current Health Legislation
Northeastern University, Boston, Massachusetts
The Role of the Clinical Laboratorian in Health Planning
the Rhode Island Society for Medical Technology

1977
Viruses: The Ultimate Parasite
Anna Maria College, Paxton, Massachusetts
Moderator: Microbiology Problem Solving Session
MAMT Annual Meeting
The Deep Mycoses: Clinical Significance and Identification
ASMT Region I Annual Seminar
Quality Control in Microbiology: Update
ASMT Region I Annual Seminar
Clinical Parasitology - series of seven lectures
Newport Hospital, Newport, Rhode Island
National Legislation Issues
MAMT Semi-Annual Meeting

1978
National Health Insurance - Inservice Education Series
Newport Hospital, Newport, Rhode Island
Critical Events in Health Planning
MAMT Annual Meeting
Microbial Genetics: Tomorrow's Pathogens
MAMT Annual Meeting
The Impact of Health Planning on the Laboratory Profession
ASMT Annual Meeting, Chicago, Illinois

1979
National Health Planning
ASMT Annual Meeting, Las Vegas, Nevada
Moderator: Health Issues
ASMT Annual Meeting, Las Vegas, Nevada
Clinical Significance of Recent Advances in Microbial Genetics
Maine Association for Medical Technology Annual Meeting
Recombinant DNA Technology: Science and Society
MAMT Annual Meeting
Involvement: A Professional Obligation
MAMT Annual Meeting
Health Planning
MAMT Semi-Annual Meeting
Clinical Laboratory Legislation
Charlton Memorial Hospital

James T. Griffith

1980

National Health Planning Issues
MAMT Annual Meeting
Health Planning
Roger Williams General Hospital, Providence, RI
Clinical significance of Recent Advances in Microbial Genetics - One Year Later
Maine Association for Medical Technology Annual Meeting
Recombinant DNA Technology: Science and Society
Rhode Island Society for Medical Technology Annual Meeting

1981

Recent Advances and Clinical Application of Recombinant DNA Technology
ASMT Region I Annual Seminar
Laboratory Regulations and Licensure in Massachusetts - requested and presented as the sole speaker at a special Meeting of the Massachusetts Public Health Association
HSA's Role in the Determination of Need Process
MAMT Annual Meeting

1982

Fundamental Changes in How We Think About Fungi
ASMT Region I Annual Seminar
The Third Generation Cephalosporins
New Hampshire/Vermont Societies for Medical Technology Annual Meeting
Opportunistic Fungal Infections
New Hampshire/Vermont Annual Meeting
The Third Generation Cephalosporins
AMT-ASMT-CLMA Joint Fall Meeting, Maine
Ethical Aspects of Recombinant DNA Technology
AMT-ASMT-CLMA Joint Fall Meeting, Maine

1983

Beta-Lactam Antibiotics: Microbiology and Pharmacodynamics
ASMT Region I Seminar, Hartford, Conn.
Workplace Hazards Involving *Cytomegalovirus*
Rhode Island Blood Center, Providence, R.I.
Sexually Transmitted Diseases.
Rhode Island Society for Medical Technology, Newport, R.I.
Pathophysiology of Tuberculosis.
St. Joseph's Hospital, Providence, R.I.

1985

Antimicrobial Resistance in the 1990's
Rhode Island Society for Medical Technology, Providence, R.I.
Methicillin-Resistant *Staphylococcus aureus*
Charleton Memorial Hospital, Fall River, Mass.
Phase and Darkfield Microscopy
Cardinal Cushing General Hospital, Brockton, Mass.
The Microbiology of Retroviruses,
ASMT Region I-AMT Eastern District Area I, First Joint Meeting, So. Portland, Maine
The American Health Care Crisis
Cape Cod Council of Churches,Hyannis, Mass
AIDS: Public Policy Issues,
Southeastern Massachusetts Health Planning and Development, Inc., Middleboro, Mass.

1986

Microbiology and Pharmacology of the Newest Antimicrobial Agents
ASMT Region I Seminar, Saratoga, N.Y.

1987
Legislation Impacting on the Delivery of Health Care Services
Bristol Community College, Fall River, Mass.
Advances and Current Use of Quinolone Agents
ASMT Region I Annual Meeting, Framingham, MA

1988
The Microbiology and Pharmacology of the Newest Antimicrobial Agents
ASMT Region I, Nashua, NH
Professionalism - Continuing Education Series
New England Deaconess Hospital, Boston, MA
The 4-Quinolones
ASMT Annual Meeting, Las Vegas, Nevada
The Microbiology and Pharmacology of the 4-Quinolones,
Massachusetts Association for Medical Technology Annual Meeting, Sturbridge, Mass
Retroviral Chemotherapeutics
Massachusetts Association for Medical Technology Annual Meeting, Sturbridge, Mass.
How to Computerize a Med Tech Curriculum
ASMT Annual Meeting, San Antonio,TX
Tuberculosis: presentation for SMU/University of the Azores Conference
Southeastern Massachusetts University, No. Dartmouth, MA

1989
Retroviral Chemotherapeutics
ASMT Annual Meeting, Washington, D.C.
Antimicrobial Agents of the Near Future
MAMT Annual Meeting, Sturbridge, MA
Microbiology and Pharmacology of Antimicrobial Agents
ASMT Region I Annual Meeting, Cromwell, CT

1990
AIDS Therapies
MAMT Annual Meeting, Sturbridge, MA

1991
CLIA '88
National Society for Histotechnology, Region I, Warwick, RI
Current Status of Legislative and Regulatory Issues
ASMT Region I Annual Seminar, Cromwell, CT

1992
Staffing the Laboratory of the Future: Key note speaker
Clinical Laboratory Managers Associations, Warwick, RI

Workshops Given:

1976
Quality Control for the Clinical Laboratory
full day workshop - development of a 50 page manual
V.A. Hospital, Brockton, Massachusetts
Basic Clinical Mycology
half day workshop - 30 page manual
ASMT Region I Annual Seminar
Medical Parasitology
full day - 70 page manual
MAMT Annual Meeting

James T. Griffith

1977 Professional Standards Review Organizations
DHEW sponsored full day workshop
Boston, Massachusetts

1982 Antimicrobial Agents: Pharmacodynamics and Microbiology
St. John's University, New York
The Beta-Lactam Antibiotics
MAMT Annual Meeting
Antimicrobial Susceptibility Testing and Clinical Relevance
ASM - Massachusetts Department of Public Health Meeting

1983 Review of Dermatophyte Mycology
Area Health Education Center (AHEC)
Advanced Diagnostic Parasitology: Identification of the Helminths
AHEC

1984 What We Know About *Legionella*
ASMT Region I Annual Seminar, Sturbridge, Mass.
Sexually Transmitted Diseases
Rhode Island Society for Medical Technology Annual Meeting

1985 What We Really Know About *Legionella*
ASMT Region I - AMT Eastern District Area I, First Joint Meeting, So. Portland, Maine

Miscellaneous Presentations:

1975 The Clinical Laboratory Improvement Act In-Service Education program for clinical laboratory, nursing and administrative staff
Newport Hospital

1976 Commencement Speaker - School of Medical Technology,
Newport Hospital

1977 Commencement Speaker - School of Medical Technology,
The Miriam Hospital
National Health Insurance - 2 parts
Southeastern Massachusetts Health Planning and Development, Inc. Meeting

1978 Article: Future Directions
The Paul Revere, MAMT Newsletter
Lecture: Basic Mycology
Bristol Community College
Public Health Issues Address: WPEP Taunton Radio Station against Roger Nelson, M.D.
sponsored by SMHPD, Inc. at the Murray Universalist Church
Panelist: Medical Laboratory Guidelines for Certificate of Need Application
MAMT Annual Meeting
Testimony: State Wide Health Plan
representative for the SMHPD, Inc.
Lecture: Medicare and the Health Planning Process
East Main Senior Citizen Drop-In Center Fall River, Massachusetts

Panelist: Career Diversification in Clinical Laboratory Science
MAMT Annual Meeting
Testimony: Laboratory Section of the State Wide Health Coordinating Council

1981 Lecture: Health Planning for Health Care
League of Women Voters Concord, Massachusetts
Developed policy paper: Recombinant DNA
Massachusetts Department of Public Health

1988 Guest, WNBH with Tim McKenna: **Medical Technology - Practice and Profession**

1992 Commencement Speaker: School of Medical Technology, The Memorial Hospital of Rhode Island, Pawtucket, RI