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Introduction

The demographic changes in the United States with its increase in people over age 65, both in absolute numbers and as a percentage of the population, has great importance to many aspects of American life. Before World War II the major changes which increased longevity were better sanitation and public health measures. Since World War II the changes have been largely the effects of new treatments of individual patients. In this issue we consider changes over the past 50 years which have increased both longevity and the quality of life for older people. As could be anticipated, new problems arise from successes, and some of these will be addressed. Since most readers will now or later fall into the category of older patients, the subject matter crosses all specialties of the Washington Academy of Sciences.

Kingsley M. Stevens
Guest Editor

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Why Geriatrics?

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ABSTRACT

Americans are growing increasingly older. Over the next 50 years we expect a significant growth in the segment of the population over age 65. This will present unprecedented challenges to our social, economic and health care institutions. Geriatrics, a relatively new field in American medicine, focuses on the health problems of the elderly.

While the maximum human life span of some 100 years has not changed over the course of time, it is quite clear that the number of individuals living into old age has increased dramatically. During the twentieth century alone the average life expectancy of Americans has gone from 47 years in 1900 to 73 years in 1980.[1] Environmental, social and medical advances in such areas as sanitation, nutrition, health behaviors, infant mortality, antibiotics, surgical techniques and cardiac care are known to have contributed to this remarkable increase in life expectancy. Demographic data show that by 1990, 32 million Americans, or 12.7% of the population will be 65 years of age and older. By the year 2030 the expectation is that approximately 20% of American population will be 65 and over.[2,3]

Among our aging population, the group over 85 years old is proportionately increasing at the greatest rate. Currently there are some 2.7 million people over the age of 85 and this group is predicted to double in size by the end of the century. Since the 1960's there has been a strong downward trend in the mortality rates for the very elderly in western society. Between 1933 and 1966, the death rate in the U.S. for those over 85 years old had declined only 10%. In contrast, the death rate for this group declined 26% between 1966 and 1977. It appears that reductions in the risk of dying from heart diseases and stroke may account for a substantial part of this change. If current trends continue, by the year 2050 half of all American may live to age 85.[4]

While the majority of older Americans enjoy relatively good health and independence, they clearly have a much higher incidence of disease and disability. Heart disease, stroke, arthritis, cancer, diabetes and obstructive lung disease are all for the most part diseases of the elderly. In a health survey performed in the city of Uppsala, Sweden by Waern,[5] the prevalence of various diseases for 50 versus 60 year old men revealed 5 times more circulatory diseases, 10 times more musculoskeletal disorders, 8 times more diabetes, respiratory diseases and cancer, 4 times as many nervous diseases and twice the number of mental disorders among the older as compared to the younger age group. The incidence of dementia, depression, hip and vertebral fracture rates, urinary incontinence, and malnutrition all increase significantly with age. Along with this high incidence of disease comes a high incidence of disability and the need for more medical, nursing, rehabilitative, home care and nursing home care. A number of health surveys have estimated the prevalence of disability to be from 3% to 18% of people between the ages of 65 to 74 years old, and from 6% to 50% of those above the age of 75.[6] Currently there are more nursing home beds than acute hospital beds, and those over 65 years old have a 20% chance of being admitted to a nursing home during the remainder of their life time.

With this weight of disease and disability it is easy to see why the elderly consume more health care services than their numbers alone suggest. Presently, the 12% of the population over the age of 65 utilizes 40% of all acute hospital beds, 25% of prescription drugs, and accounts for 30% of the nation's health care expenditures and half of all federal health dollars.[7] By the end of the century half of all health care encounters will be with patients 65 and over.

These overwhelming demographic changes challenging our health, social, economic and political institutions have been referred to as the "geriatric imperative". Given this imperative one would have expected the American academic medical community to have championed the cause of geriatrics and gerontology, and to have produced a large cadre of clinicians and researchers interested in geriatrics. In spite of the need this has not happened, and for most medical students and postgraduate physicians in training there is little if any formal training in geriatrics. This is particularly ironic since it was Ignatz Nascher, an American pathologist, who is credited with coining the term geriatrics in his 1914 text book *Geriatrics: The Diseases of Old Age and Their Treatment*. But today, some 75 years later, the study of geriatrics is still new to American medicine.

In Great Britain the importance of geriatrics has been formalized by it's recognition as a medical specialty. There are established academic departments in half of the medical schools, formal curricula in 93%,[8] postgraduate specialty training in geriatrics, hospitals specializing in the care of the elderly, and certification and consultant status for physicians trained in geriatrics.

Geriatrics developed in Great Britain in the 1930's when Dr. Marjory Warren and several other physicians began to take an active interest in the patients on the long term care wards of the hospitals. They came to appreciate that there was much to learn from these chronically ill and frail elderly patients whose problems had been viewed as beyond the scope of medical practice. These were patients with severe strokes, dementias, neurological disorders,

and other chronic disabling diseases who had often been viewed as medical failures. It was from this attempt to uncover previously overlooked medical problems and to find practical approaches to dealing with the disabilities imposed by chronic diseases that the field of geriatrics grew in the United Kingdom.

In the United States modern academic medicine has concerned itself largely with basic science research and technological development. We have been fascinated by high technology topics such as lasers, coronary by-pass surgery, magnetic resonance imaging, monoclonal antibodies, and gene splicing. It is only in recent years that American medicine has begun to address geriatrics.

In reaction to the demographics of aging it has been the political and social leaders, and a few evangelical senior academic physicians who have pushed for the academic medical community to take an interest in aging.

One of the most important events in the development of American geriatrics was the passage of the 1974 Research on Aging Act authorizing the establishment of the National Institute of Aging as one of the National Institutes of Health. The NIA has become a leader in the effort to get geriatrics into the mainstream of American medicine. During the past decade there has been significant growth in geriatrics. A number of medical schools and hospitals have established divisions of geriatrics with clinical and research faculty, and fellowship training programs. In 1988 the first examination for special competency in geriatrics was given jointly by the American Board of Internal Medicine and the American Board of Family Medicine. The vast majority of those taking the exam were practicing physicians without formal training in geriatrics.

Kane[9], in a 1980 Rand Corporation study of geriatric manpower needs, estimated that in order to have enough geriatricians just for academic positions and as consultants in practice, we would currently need about 8000 specialty trained physicians. Several surveys of physician members of the American Geriatrics Society and the Gerontological Society of America have estimated the number of physicians who consider themselves geriatricians to be in the range of 750 to 1200, and only a quarter of these could be considered as full time academic faculty. In 1987 there were 66 geriatric medicine fellowship programs graduating approximately 100 trained geriatricians per year.[4] It is clear that these numbers fall far short of what is needed if geriatrics is to be established as significant presence in American medicine. The training of geriatricians has been severely limited by program funding, number of programs, availability of faculty and dearth of qualified applicants. The problem of recruiting physicians to train in geriatrics is difficult because of a lack of exposure to formal geriatrics during medical school and residency, negative steroetype images of the elderly, and comparatively low Medicare reimbursement for the time consuming physician visits which are typically needed in evaluating elderly patients.

The argument has been made that since physicians (especially internists) who treat adults treat a large number of elderly patients, there is no need for geriatrics as a specialty area. But just as there are significant anatomic, physiologic and clinical differences between children and adults, there are signif-

icant differences between 40 year old and 80 year old.[10] Important physiologic and functional changes occur in most organ systems with aging. While it has often been difficult for researchers studying the biology of aging to differentiate normal age related changes from disease related changes, a number of significant age related changes have been identified. The heart and lungs are two organs systems which illustrate age related changes and their clinical significance.

In the heart there are sclerotic and calcific changes which occur principally in the high wear areas of the aortic and mitral valves. These may lead to aortic stenosis and mitral insufficiency. Calcification also occurs in the electrical conduction system of the heart and may lead to abnormalities in heart rhythm. The pacemaker cells of the heart are reduced both in number and rate of firing and there is slowed conduction through the heart's electrical conduction system. There is a reduction in response to adrenergic stimulation. Although it is unclear whether this reduced response is because of a decline in the number or function of the receptors, the result is seen in the increased sensitivity of elderly individuals to antagonist medications such as beta-adrenergic blockers and channel blockers. Physiologically healthy older people have been found to have decreases in maximum stroke volume, cardiac output, oxygen uptake, and maximum heart rate in response to exercise.

The respiratory system shows some of the greatest age related changes. The chest wall becomes increasingly more rigid and less compliant. The lungs lose elasticity and there are fewer alveoli to effect gas exchange which results both in ventilation perfusion mismatching and reduced gas diffusing capacity. While total lung capacity remains relatively constant with age, residual lung volume increases and there are marked decreases in airflow rates which become most prominent in response to exercise. Lung defenses are also altered by reduced cough force, impairments in mucocillary cleaning of the upper airways, and the response of macrophages, lymphocytes and neutrophils to bacteria and other antigens. The result of these changes, compounded in many cases by smoking and environmental pollutants, leads to the increased incidence of pneumonia and chronic obstruction pulmonary disease in the elderly. However, in spite of this decreasing respiratory capability, training and conditioning can result in high levels of fitness.

While research into the biology and physiology of aging is key to the future development of geriatrics and gerontology as a discipline and scientific data base, it has been in the clinical arena that geriatrics has been most active and faces it's greatest challenges. The elderly and the frail elderly in particular have their own set of rather unique problems which are rarely well addressed by the mainstream of medicine. In addition to the high incidence of the diseases mentioned above, there is a high incidence of gait disorders, falls, urinary incontinence, dementia, depression, delirium, hearing and visual loss, skin pressure ulcers, osteoporosis, adverse drug reactions, excessive medication use, psycho-social dysfunction and ethical treatment dilemmas. A number of these problems are frequently overlooked, and for many there is no clear and effective therapy.

Urinary incontinence serves as a good example of such a problem. It is a major health problem of the elderly estimated to affect 10 million American adults and conservatively costing 10 billion of dollars per year[11] in home, hospital and nursing home expenses. It is a disruptive disorder which can lead to urosepsis, falls, rashes, skin breakdown, social isolation, embarrassment, loss of independence and often to nursing home placement. Although several studies have demonstrated that combined medical and behavioral therapy predicated on specific diagnosis can be effective in yielding a number of patients either continent or substantially drier, most patients receive no systematic evaluation. In a 1987 study of incontinent health related nursing home patients, Zirker[12] found that although these patients had been incontinent an average of two years, only 16% had ever received a systematic evaluation to diagnose the problem. After medical and functional assessments, half of the patients were clinically improved using behavioral techniques and drug therapy. However, in order to carry out such a program the combined efforts of physicians, nurses, social workers, and physical therapists were required.

In an attempt to deal with such complex problems and disabilities, geriatrics has recognized the need to go beyond the traditional medical model of disease. For many chronic diseases such as diabetes and stroke, it is the resulting disability, rather than the disease itself, which diminishes the quality of life. While organ damage cannot usually be reversed, the functional disabilities and quality of life can frequently be improved through physical therapies and nursing care. Geriatrics has employed batteries of cognitive and functional assessment tools, and interdisciplinary teams of health professionals to evaluate and coordinate the care of frail elderly patients. It is from this perspective that the concept of geriatric assessment teams and geriatric evaluation units for both inpatients and outpatients has grown. The Veterans Administration has been a leader in geriatrics and has established many such units. The purposes of these units is to evaluate frail elderly patients, uncover previously overlooked diagnoses, dementias and psychiatric disorders, provide medical, nursing and rehabilitative care, and coordinate services so that, whenever possible, patients could return home. Although the goals and basis for such units appears to be sound, their cost effectiveness remains to be proven.

Conclusion

To provide good quality care for frail elderly patients is clearly an expensive and very labor intensive activity. From the demographics of aging it is obvious that there will be increasing need for hospital, nursing home, outpatient and home care services. Given the "geriatric imperative", it is logical to develop geriatrics into a field of medicine capable of producing researchers, teachers and clinicians, who can provide the leadership needed to meet this challenge.

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Where Technology Fails

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ABSTRACT

While medical science has made amazing progress over the past half-century, clinical applications have fully solved only a small number of diseases. Hence blind application of all of our technology not only will not halt these diseases but will produce many complications, medical and otherwise. In our society, the individual patient should make his own informed decisions on how much technology is appropriate for him. These decisions are needed for specific medical situations and for more general areas such as "Do not resuscitate orders" and "hospice" care.

One hundred and forty years ago, a prominent Boston physician vividly presented a central concept for geriatrics. His presentation was non-medical, but highly appropriate. Oliver Wendell Holmes, in "The Deacon's Masterpiece" or "The One-Hoss Shay," described a chaise which lasted without repairs for 100 years to the day, then disintegrated. One section goes like this:

> Now in building of chaises, I tell you what,
> There is always *somewhere* a weakest spot,
> In hub, tire, felloe, in spring or thill,
> In panel, or crossbar, or floor or sill,
> In screw, bolt, thoroughbrace, lurking still,
> Find it somewhere you must and will,
> Above or below, or within or without,
> And that's the reason, beyond a doubt,
> A chaise *breaks down*, but doesn't *wear out*.

This is certainly the way to live in old age! Holmes picked a time span for the chaise of 100 years, the actual life span attained by a few people, so the analogy as an ideal is realistic and probably intentional. It has often been stated that an objective in geriatric care is to "add life to the years, not years to the life." This emphasizes the concept of functional ability even though it may be at the expense of a longer life span.

The objective of the deacon, so well carried out, was to have the chaise remain integrally sound for a long time and then collapse *in toto*. No one is really expecting medical technology to provide people with functional integrity for 100 years and then suddenly die. The preceding papers have briefly described ways in which medical and dental programs have helped older people approach this goal. The key to this progress has been technology and Jennett has written a good overview of high technology.[1] If the advances enabling patients to retain or regain full function had kept pace with the advancing longevity, the impact of technology would be overwhelmingly beneficial. This has not happened. Technology is much more successful at making precise diagnoses and at keeping people alive than in restoring them to full function. Consider those polar extremes. At one end are the prosthetic devices such as eyeglasses and contact lenses. They are tremendously effective and enable users to be almost 100% functionally effective in vision. However, they do not cure the visual defect and they are a nuisance. The decision on the benefit is clear; the technology should be, and is, extensively used. At the other extreme is the demented patient who has had several strokes and is kept alive for years on respirator, feeding tube and antibiotics. The technology is "effective" but of negative value. Hence this technology should not be used, but it is used. The United States leads the world in the percentage of its population who are over age 85. While many of this group are highly functional, far too large a number lead a vegetative existence due to technology. These examples are extremes and most technological applications will not offer such clear choices.

The development and application of medical technology follows a certain sequence. First, the question is raised as to whether a certain procedure or effect can be carried out. Research and development follow which provide a "yes" answer. Once available to physicians, the approach is "Since it is available, it may be desirable to use it." Soon this changes to "If it can be done, it should be done." Usage expands and, all too soon, the stage of the technological imperative has arrived which says, "If it can be done, it MUST be done." There are, of course, clear medical contraindications to diagnostic and therapeutic interventions. Yet the overwhelming pressure is toward the technological imperative. To some degree, it comes from patients and families. But in the United States the major players are the medical profession, which is extremely technologically oriented, and the legal profession, which often appears ready to turn any omission of a diagnostic or treatment procedure into a malpractice claim. Hence in this country, medical care runs largely on the technological imperative.

Application of technology will increase longevity and American courts have often ruled that length of life is vastly more important than *any* other consideration. The desires of the spouse and other family members are usually ignored by courts; the only person who can say "no" is the patient. Court rulings throughout the United States in both state and federal courts have established the right of a competent patient to accept or refuse any type of treatment or life support system. This position is basically sound, but often a formerly competent person is not competent when the decision concerning

his care must be made. Emphasis on self-determination then turns from an asset to a liability, since many courts will not accept "substituted judgment" by the patient's representative.[2] In operational terms, this means that even if you felt very strongly that you did not want to exist in a severely disabled state, you might well be forced by law to exist in that state for many years.

The answer to this problem is by writing a "living will" or "advance directive" which specifies in reasonable detail what you do or do not want and under what circumstances. Since certain states refuse to accept tube feedings as a medical treatment, it is very important to specify that you refuse forced feeding by tubes or intravenous methods under certain circumstances. However, no advance directive can be both broad enough yet contain enough specifics to cover the large range of actual situations which may arise. Hence you should also complete a form often titled "Durable power of attorney for designation of health care agent." The individual(s) so designated will make specific medical decisions consistent with the general provisions of your advance directive. Both documents should have witnesses and be notarized. Neither of these documents are fully accepted by all states. Irrespective of their "official" status, they demonstrate clearly that you have considered this problem and reached definite conclusions and that the individual selected to make decisions knows of your wishes and expects decisions to be made along the lines you determined when competent.[3]

Important as they are, such advance planning does not in itself resolve ongoing medical decisions which we all face in varying degrees. The pervasive technological imperative will be urging us on. How does one make a logical decision? As a scientist, the reader knows that the way to make medical decisions is to obtain the needed facts and be able to interpret them. Faith in technology often dominates the facts on technology: Consider the facts about cardiopulmonary resuscitation (CPR) and do not resuscitate orders (DNR).

The application of effective CPR using electrical defibrillation began in 1962 with patients who had acute heart attacks who were on EKG monitors. Many had episodes of cardiac arythymmias, some of which were ventricular fibrillation producing cardiac arrest. These patients were essentially dead, but about half of them resumed cardiac function following CPR. Since the patients were constantly monitored, CPR began within seconds of the arrest. Here we have the original technological advance with appropriate application under specific conditions. Its application under these circumstances quickly spread. Soon it was being used on non-monitored cardiac patients as well; then on non-cardiac patients. Malpractice suits soon emerged when patients died from any cause and were not given CPR; this vastly increased the numbers of patients who received CPR. By the 1980s most patients who had a cardiac arrest when in a hospital received CPR unless they specifically requested a DNR order. The technology of CPR had clearly reached the state of the technological imperative. It could be done and it was done. That was not the end. In New York State, the legislature passed a DNR law so that doctors could be absolved from liability if they withheld CPR under defined conditions. These were highly defined conditions: The order could only be written for terminal patients, it had to be reviewed every three days and there were other strictures.

Since the law specified what was required so as *not* to be liable, it in effect also specified that if the doctor did not provide CPR when a DNR order was not in place, then he may be liable. Hence since 1988, a technological medical procedure has been demanded by state law.

State laws may require other technological procedures such as immunization against certain diseases before entering grade school. The above terse history covering 26 years would certainly imply that CPR was an extremely valuable technology which should be widely utilized. But how effective *is* CPR? For the type of patients for which it was developed, about 30% of those receiving CPR leave the hospital alive. For other groups, the results are much less successful. Many will have cardiac function partially restored but few will leave the hospital alive. The time lapse from cardiac arrest to defibrillation is extremely important, with much higher survivals when the time is less than three minutes. Patients who have sepsis, pneumonia, cancer and renal failure have almost no survivors from CPR and older patients, as a group, fare very poorly.[4–8] The facts on CPR today are that most patients receiving CPR attain only added misery. The rigidity of legal requirements makes it very difficult to apply this valuable technology as it should be applied.

An escape from the technological imperative can be by use of palliative and "hospice" type programs. The shift in emphasis is to couple length of life more closely with the quality of life. The technological imperative, in practice if not in theory, almost invariably comes out favoring length of life over quality of life, so leads to frenetic activity to the very end. This does not happen in the hospice type programs in the United States.

The need for an "escape hatch" from current mainstream medical practice is due to society's views on two subjects: Liability litigation and refusal to accept death. True malpractice certainly exists, but the number of malpractice suits filed in the U.S. is totally out of line with actual malpractice. These charges are so frequent that a doctor is almost forced to act as though every episode of illness he treats must be treated as though he will be sued. A malpractice lawyer might claim this is as it should be. It is not. This approach is incredibly expensive for society. At the individual level, each patient is forced to undergo all that technology can muster, often repetitively. American views on death set the stage for the American scene. Our society does not accept death as part of the natural order. Our society also has great faith in technology (even though society is not infrequently very anti-scientific!) The combination demands that medicine see death as the ultimate enemy and technology the way to defeat death. Given American views on litigation and death, it is small wonder that physicians as a group do everything possible to extend life, no matter what. Many social trends have shaped this view toward death. Low death rates, most people dying in hospitals and widely scattered families, all make death unfamiliar to Americans. In addition, Americans traditionally take the view that everything can be improved, so everything should be tried to forestall death. Yet in 1989, as it has for billions of years, death comes to every living organism.

The need for a haven from the dominant societal pressure for frenetic activity to the very end is all too real. That need has not been adequately met

but the hospice concept of care is spreading and there are now about 2,000 hospice programs in the U.S. The patient accepts that there is no more specific treatment which might cure or arrest his progressive disease. The patient desires to be free of pain and have his other symptoms controlled so that he can continue to maintain maximum independence and maximum social interactions until he dies. These goals are surprisingly hard to meet in both acute hospitals and nursing homes. For most hospice programs, the patients is not expected to survive over six months. Because of the nature of the disease, cancer patients make up the large majority of hospice patients. But certain patients with advanced heart, lung or liver disease, and those with advanced AIDS are also appropriate.

The term "hospice" as used in medieval Europe often referred to rest houses supported by religious groups where pilgrims, en route to an important religious site, could find food, lodging, rest and some nursing care. Refreshed and remotivated, the pilgrims continued their journey. Today, as then, the hospice is a way-station, a place of rest and relaxation for the sick as they travel to the end of their personal journey. The involvement of third-party payers had led to rigid definitions of their requirements for a hospice. It is ironic that both federal and state regulations define hospices as being primarily an "at home" function, while in the original definition the pilgrim was far from home. Since hospice care is a concept of care, the term is appropriate whether the care is given primarily in the home or in a hospital or other institution. Home-based programs utilize many community volunteers which enhances this type of hospice program and the home model is the ideal type. The National Hospice Organization (U.S.) has prepared this definition:

> Hospice is a medically directed, nurse coordinated program providing a continuum of home and inpatient care for the terminally ill patient and family. It employs an interdisciplinary team acting under the direction of an autonomous hospice administration. The program provides palliative and supportive care to meet the special needs arising out of the physical, emotional, spiritual, social and economic stresses which are experienced during the final stages of illness and during dying and bereavement.

Since death is the expected outcome for hospice patients, the staff does not view death as representing failure. The staff is well satisfied if they can provide a good quality of life leading to an easy death. If the person can come to terms with his death and find renewed support from family members, some previously alienated, so much the better. The team spends much time with family members to reach the objectives. The nurse, especially, must play multiple roles. She or he needs to know current technical options, although the nurse may not apply many of them. The nurse needs to understand the steps of adjusting to death and dying and interact with the patient as he works his way through the process. Team members need time to listen and talk with the patient far more than happens for most patients today. "Standard protocols" are often inappropriate for hospice patients and nurse and physician must be ingenious and flexible in developing individual solutions to promote physical and emotional comfort. All this should be done with the patient

actively participating in decision making. A sense of humor is especially helpful in hospice-type programs. These programs can lead to surprisingly contented patients despite their destructive diseases; visitors to our hospice often comment on the cheerful appearance of our patients.

Conclusions:

1. Medical technology has two sides. While designed to decrease disability and suffering, at times technology increases both of these.
2. The technological imperative is prevalent in this country and often inappropriate. Some of its negative effects can be countered by the preparation of "living wills" and "durable power of attorney" documents.
3. For many terminally ill patients, a hospice-type setting will provide superior care to an acute hospital.

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Antibiotics and the Older Patient

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ABSTRACT

Effective antibiotics were introduced in 1935 and the field has expanded steadily since then. Their application has influenced almost every aspect of medicine, either directly or indirectly. Because of this pervasive aspect, antibiotics have been the most important single determinant of improved medical care for older patients over the past half century. In the 1980s, the bacteria causing most infections in hospitalized patients are not classical pathogens but normal flora growing in abnormal locations. This had led to widespread use of antibiotics active against many species of normal flora; this extensive usage has led to the emergence of many resistant strains of bacteria. Approaches to lessen damage to normal flora and also decrease the development of resistant microbes are presented.

Use of Antibiotics

Statistics on the causes of death in the United States are available over the 1900–1985 period.[1,2] These data are not directly comparable over time due to changes in classification, changing age distribution and improved diagnostics. Despite these factors, the major trends are clear. It will be a surprise for many to find that not only today, but even in 1900, the largest cause of death was cardiovascular. After that, however, the 1900 picture was dominated by infectious deaths: Pneumonia, influenza, tuberculosis, enteric infections, diphtheria, measles. By 1935 the frequencies of all these diseases had fallen, especially the enteric infections. Although the death rate for syphilis had not changed greatly from 1900, in 1935 it was among the top ten causes of death.

In 1985 the overall death rate was 874/100,000 population. Heart disease accounted for 37%, cancer for 22%, stroke for 7% and chronic obstructive lung disease for 4%. The only infectious disease producing more than 1% of

deaths was pneumonia, listed at 3%.[2] From these mortality data, it would appear that bacterial infections are not now a major problem as causes of death. The amounts of antibiotics used today are immense and at great cost. What have antibiotics done, how are they being used today and what appears ahead?

Social changes, better hygiene and sanitary engineering were the major causes of decreases in tuberculosis and enteric infections produced by *Salmonella* and *Shigella* species. However, antibiotics have effectively treated most of those cases which did develop. Antibiotics have been highly effective against pneumococcal pneumonia, streptococcal infections, gonorrhea, meningitis and syphilis. They have cured innumerable cases of bacterial infections of the lungs, bladder and other internal organs. Antiseptic technics made major surgery possible and remain a critical requirement. Nevertheless, antibiotics have also greatly increased the ability to carry out surgery on patients formerly considered at too high risk. They have also provided effective treatment of local and systemic infections which occur following surgery.

Drug treatment of rickettsial infections such as typhus and Rocky Mountain Spotted Fever works well but drug treatment for viral infections is still primitive. However, antibiotics have played a major role in the development of viral vaccines. The major technical problem for such development was obtaining large supplies of purified virus. Some viruses, such as influenza virus, could be grown in adequate quantities in chick embryos although purification remained a problem. But most viruses required the development of tissue culture technics. These were begun by Alexis Carrel before World War I and were successful at the laboratory level because of his extreme methods of maintaining sterile conditions. However, commercial development was impossible without antibiotics. Addition of antibiotics to the medium prevented destruction of the tissue culture cells by the ubiquitous contaminants. This led directly to viral vaccines, both killed and attenuated.

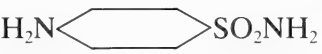
When organ transplantation began, there was need to depress the immune system to prevent rejection of the transplant unless it was from an identical twin. We now have very effective immunosuppressive drugs, but they could not be used if antibiotics were not available. Chemotherapy of most forms of cancer is widely used in the United States. Since these drugs almost invariable depress host responses to infections, their use also depends on antibiotics.

The Antibiotics

We have presented the successes of antibiotics without any consideration of their history, how they act and how the bacteria react. The word "antibiotic" is defined as "a substance produced by a microorganism and able in dilute solution to inhibit or kill another microorganism." It is now over a half century since the first really satisfactory antimicrobial drug was introduced. That was in 1935 and the drug was an azo dye named Prontosil. The azo dyes containing a sulfa nucleus were developed by the I.G. Farbenindustrie as dyes which bound very tightly to the proteins of wool and silk. Their synthesis began in 1909 and soon afterwards it was suggested that these dyes might also bind

tightly to bacterial proteins and thereby inactivate them. Twenty-five years passed before Domagk demonstrated that mice would be protected from experimental streptococcal infections with Prontosil. Soon after, French workers found that in mice and other mammals the azo bond was cleaved and the active agent was sulfanilamide, shown below:

We now know that the mode of action of sulfa drugs is not by binding of bacterial proteins but by competitive inhibition of para-amino benzoic acid (PABA), shown below:



PABA is one of three major precursors of the vitamin folic acid. Sulfa drugs inhibit those microbes which must synthesize folic acid as they have no transport mechanism whereby extracellular folic acid could be taken into the cell.

The first true antibiotic was penicillin and its history is well known. Although Fleming described its antibacterial effects in 1929, the instability of penicillin and the small amounts produced delayed commercial production until these problems were solved by British and American teams in World War II. The toxicity of penicillin G is so low that the lethal effect of huge doses is due to the cation in the salt, potassium or sodium. This pharmacological inertness for mammalian cells reflects penicillin action on cell walls, which mammalian cells lack.

Since the "antibiotic era" began, between 5,000 and 10,000 natural antibiotics have been described and between 50,000 and 100,000 semi-synthetic analogues have been made! Yet fewer than 150 antibiotics are available commercially in the United States. In 1986, 29 of these were naturally occuring with the remainder being either partially or totally synthesized.[3] Antibiotics can be grouped by mode of action, shown in Table 1:

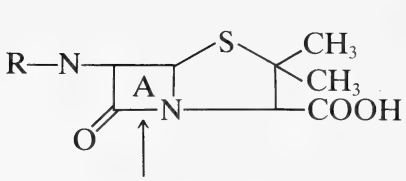
Table 1.—Major antibacterial agents.

Mode of action	Examples
Inhibition of cell wall synthesis	All penicillins All cephalosporins Vancomycin
Inhibition of nucleic acid synthesis	Quinolones (e.g. nalidixic acid, ciprofloxacin)
Inhibitors of ribosome function	Streptomycin Gentamicin Tetracycline Erythromycin
Inhibitors of folate metabolism	Sulfa drugs Trimethoprin

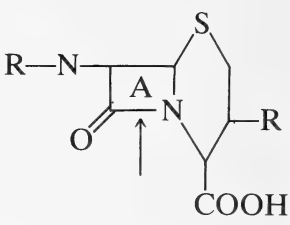
The penicillins and the cephalosporins have been the least toxic of the antibiotics and they share a β-lactam ring, the active group, which is labeled "A" in the structural formulae.

General Formulae

Penicillin



Cephalosporin



These two groups of antibiotics, plus new groups called the carbapenems and the monobactams, comprise the β-lactam antibiotics. The β-lactams dominate development work in antibiotics. Cephalosporins have greater changes in activity than penicillins when side chains are modified. The mode of action of all β-lactam antibiotics is the same. The bacterial cell wall is synthesized by enzymes on the cell membrane. The β-lactam ring, on interacting with a specific bacterial membrane bound peptidase, opens at the site of the arrow and binds to the enzyme, inactivating the enzyme and thereby halting cell wall synthesis.[4]

Bacterial Infections Today

The general concept of a bacterial infection in 1935 was that you "caught it" from another person, as occurs today with such minor virus infections as colds or a major one such as AIDS. Pneumococcal pneumonia, streptococcal sore throats, scarlet fever, diphtheria, whooping cough, gonorrhea, syphilis and local infections with *Staphylococcus aureus* followed this pattern. These still occur, but in much smaller numbers, and in 1989, the bacteria we deal with in hospitals are primarily the opportunistic normal flora of man. Normal flora are those species found on skin and in the respiratory, digestive systems and the genital tract in a high percentage of normal people. These bacteria rarely produce disease in people without risk factors. Yet these bacteria now comprise the vast majority of isolations from hospitalized patients who, through debilitation or various treatments, become at high risk for infection. Many of the strains are not "caught" from another person; they are from the normal flora of the infected patient, with the bacteria now growing in an abnormal site. The bacterial groups and culture sites appear in Table 2.

Table 2.—Bacterial isolations in the clinical microbiology laboratory at the Northport VA Medical Center during 1988.

Bacterial Type	No. of isolates	Normal location	Cultured from
Enteric bacteria	2484	Colon	
Pseudomonas sp.	520	"	urine>sputum>wounds/abcesses
Escherichia coli	503	"	urine>wounds/abscesses>blood
Enterococci	490	"	" " "
Proteus sp.	279	"	" " >sputum
Other gram-neg bacilli	692	"	" " "
Staphylococcus aureus	685	Nose	wounds/abscesses>sputum>nose
Staphylococcus coagulase negative	314	Skin	blood>urine>wounds/abscesses
β-streptococci	158	Upper resp. tract	wounds/abscesses>sputum>throat
Pneumococcus	72	"	sputum>blood
Hemophilus sp.	71	"	sputum>throat

The isolates were predominantly normal enteric bacteria found in other locations. *Staphylococcus aureus* has always been a prominent pathogen[5] especially of wounds and abscesses. The *Staphylococcus* coagulase-negative group primarily represent *S. epidermidis,* the universally abundant normal skin microbe. But it also includes *S. saprophyticus,* found in bladder infections and other newly defined species.[6] In the past, blood cultures which grew out *S. epidermidis* usually represented contamination from the skin. In contrast, many positive blood cultures today represent true bacteremias by this organism.[7] This marked change in pathogenicity is due to two factors. *Staphylococcus epidermidis* colonizes foreign bodies very effectively, rarely establishing itself internally without a foreign body as a primary site. The number of foreign bodies used today is extensive: Permanent ones, such as prosthetic joints and heart valves, vascular grafts, pacemakers, cerebrospinal fluid shunts, peritoneal dialysis catheters, and temporary intravascular catheters which now constitute almost routine care.[5] The other major change is that *S. epidermidis,* formerly sensitive to penicillin and many other antibiotics is now often resistent to not only penicillin but to many other antibiotics also.[6] This brings us to the problem of antibiotic resistance.

Antibiotic Resistance

Microbial resistance was first noted in 1913 when Paul Ehrlich reported that certain strains of trypanosomes were not killed by usually lethal concentrations of a dye, and these strains did not take up the dye. Biochemical studies on the basis of antibiotic resistance began with penicillin, with the penicillin-destroying enzyme, penicillinase, being described even before penicillin was used clinically![8] Strains of *S. aureus* produced this enzyme which was later shown to cleave the β-lactam ring. Beta-lactamases have been isolated from many species but none from pneumococci or β-hemolytic streptococci, which therefore remain highly sensitive to penicillin. For *S. aureus,* however, pen-

icillinase production has become the normal with 93% of our hospital strains doing so and 83% of community strains.[9]

By altering side chains near the active site of the β-lactam ring, penicillins resistant to penicillinase action have been produced. The first commercially successful one was methicillin, marketed in 1960. But even before being used, methicillin-resistant *Staphylococcus aureus* (MRSA) strains had been found.[9] These MRSA strains were first noted in England and spread rapidly in Europe with 34% of strains being MRSA in Denmark in 1968. However, by 1980, the percentage of such strains in Denmark had fallen to 2%[10] and fell to <1% in 1986.[11] Australian hospitals reached peak MRSA values of about 35% in 1982,[12] which figure was not attained in Italy until 1987.[13] Emergence of MRSA strains began in the U.S. in 1967 with waxing and waning in different areas. In our hospital, the percentage of MRSA strains stayed between 10 and 20% from 1981 through 1987. In 1988 there was an abrupt rise to 42% which in 1989 is beginning to fall. The actual 1988 percentage of resistant strains was probably nearer 35%, the maximum figure found elsewhere, since the 42% figure included large numbers of cultures taken specifically to trace the spread of MRSA. Epidemic strains have been described[14,15] and such sudden fluctuations probably reflect introduction of such strains. As others have found[14,16] these MRSA strains are often multiply resistant. Our 1988 results showed the following percentages of MRSA strains resistant to: Cephalothin 42%, clindamycin 41%, erythromycin 48% and gentamicin 35%. Very little resistance was found to the heavily restricted drugs chloramphenicol (3%) and vancomycin (0%) or to the new drug ciprofloxacin (3%). The older trimethoprim/sulfamethoxazole combination showed 20% resistant strains. These drugs represent all major modes of action (Table 1). Hence, many different biochemical changes, directed by DNA, have taken place in these resistant bacteria. Many of these mechanisms have not been thoroughly worked out but Neu[4] presents much current information.

As noted earlier, *S. epidermidis* has developed multiple resistance, overall more so than *S. aureus*.[6,9] Our 1988 figures confirm this, with 70% of *S. epidermidis* isolates from foreign body sources being resistant to oxacillin (methicillin equivalent), 70% to cephalothin, 58% to clindamycin, 68% to erythromycin and 57% to gentamicin. Aside from vancomycin, the *S. epidermidis* are much more often resistant to those antibiotics now most often active against *S. aureaus*: Chloramphenicol with 22% of *S. epidermidis* isolates resistant vs 3% *S. aureus,* ciprofloxacin, 12% vs 3%, trimethoprim/sulfamethoxazole, 51% vs 20%. The primary drug used to treat these multiply resistant staphylococci of both species is vancomycin. This antibiotic was isolated 30 years ago but has been little used due to toxicity and cost. Although vancomycin inhibits cell wall synthesis, it does so by direct attachment to a cell wall chain during synthesis, preventing completion of the chain.[17] Recently a strain of *S. epidermidis* has shown vancomycin resistance.[18] To date, no strains of *S. aureus* are vancomycin resistant[9] but it is probably only a matter of time before some appear.

Bacterial resistance to antibiotics is genetically determined but through two mechanisms. Chromosomal mutations are the normal genetic mechanism for

all types of cells, including bacteria. But much of bacterial resistance is transmitted by DNA outside the chromosome in particles called plasmids. Spread by this mechanism can be much more rapid than by chromosomal mutation since the plasmids can be taken up by other bacteria, sometimes even of different species. Although spread by plasmids is more rapid than through chromosomal transmission, it is less stable. Bacteria contain a chromosome but lack a nuclear membrane. Hence incorporation of information from cytoplasmic DNA into the genome is not infrequent. In the staphylococci, the production of penicillinase was originally plasmid directed but it is now incorporated in the genome of most strains. Methicillin resistance was also plasmid linked, but it too appears incorporated into the genome in certain strains.[4,19,20]

Resistance to penicillin and ampicillin is present in about 90% of both staphylococcal species in our hospital isolates. Since antibacterial agents active against penicillinase producing staphylococci are very widely used in hospitals, why have the methicillin resistant strains of *S. aureus* peaked at about 35% and those of S. epidermidis at 70%? To answer this, we must first address another question: Do MRSA strains produce more or less severe disease than methicillin-sensitive strains (MSSA)? No study presents MRSA as producing more severe disease but several reports claim that MRSA and MSSA are equally virulent.[12,14,16] Clinical studies of such infections cannot have controls, so animal studies are important. The best such study was by Peacock *et al*[14] who isolated two MSSA and one MRSA strain from patients and determined relative virulence for them plus an American Type Culture Collection standard strain. Using both intravenous and intraperitoneal injections into mice, they found no marked differences amongst the strains. Despite this, most reports and reviews consider MRSA and other resistant bacteria less virulent than sensitive strains.[9,19,21] Relative frequencies of MRSA compared to MSSA strains in specific infections also support the greater virulence of the sensitive strains: The ratio of MSSA/MRSA in 39 cases of complications of bacteremia was 12:1,[22] the ratio in 22 cases of bacteremia in AIDS patients was 11:1,[23] in 400 cases of *S. aureus* bacteremia the ratio was 133:1![24] Even when MRSA cases are specifically reported, the number are small: A pediatric study covering seven years recorded only 20 cases, primarily from intravascular catheters[16] as is found with the normally non-pathogenic *S. epidermidis*. A report on MRSA in pulmonary cases presented only nine cases.[25]

The reason that multiply resistant bacteria have not more extensively replaced sensitive bacteria and are, overall, of lower virulence, appears due to the fact that they do not grow as well.[8,18,21,26] The acquisition and maintenance of resistance factors will increase the energy requirements of the bacterial cell compared to the "wild" (sensitive) type. Hence, unless the selective pressure of the specific antibiotic is constantly present, the plasmid or the chromosomal mutation will be lost[19,27] as the sensitive type is subjected to positive selection by its faster growth rate.

Production of bacteria resistant to most antibiotics is fairly easy in the laboratory by growing the bacteria in increasing concentrations of the antibiotic. Under such circumstances, the bacterium is grown in its ideal medium

with the only restraining influence being the antibiotic. The selective conditions in clinical situations are very different. The antibiotic concentration is widely variable in place and time. Perhaps more importantly, the many host resistance factors and the geneal biochemical mileau of the host will often select positively for the sensitive strain while the antibiotic is selecting positively for the resistant strain. Particularly if isolates from a large number of hospitals are pooled, it may appear that there is almost no increased resistance from the use of antibiotics.[28] Due to the factors noted in this and the preceding paragraph, resistant strains are always in a state of flux. It is clear that clinical use of antibiotics does increase resistance.[4,29] Our hospital laboratory followed resistances of three species to three different β-lactam antibiotics over the 1981–1988 period. *S. aureus* tested against oxacillin showed 8% resistant strains in 1981 which rose to 17% in 1982. It remained between 10 and 20% until 1988 when it rose to 42%. *Escherichia coli* in 1981 had 20% of strains resistant to ampicillin. This rose to 50% in 1984 but fell to 30% in 1986 and has remained there. *Pseudomonas* sp tested against ceftaxime had only 8% resistant strains in 1981 which showed little increase through 1983. The figure then began to rise so that in 1988, 66% of strains were resistant.

As was noted earlier, methicillin-resistant *S. aureus* peak at about 35% of the total strains while *S. epidermidis* reaches about 70%. This large difference probably reflects the additive effects of two factors. Since *S. epidermidis* colonizes everyone, staff and patients alike, the pool for new mutants and plasmids is much greater. The vast quantities of antibiotics used in most hospitals ensure that all people spending long hours on a hospital unit will have much skin exposure to antibiotics. In addition, the skin has fewer immune systems at work than the wounds and abcesses where *S. aureus* abounds.

Antibiotics and the Older Patient

Although this heading is the title of the article, so far we have dealt with general features of antibiotics, microbes and patients without regard to age. In actual clinical practice, patients over age 65 largely determine the course of events in antibiotic use. Not only are their numbers rapidly increasing but they are the group with repeated hospitalizations. Catheters, especially urinary catheters, are much more frequently used in this group. They populate the nursing homes which are rife with resistant bacteria.[30] Carcinomas are more frequent over age 65 and most types increase linearly with age.

The medical-pharmaceutical complex is at war with the normal flora of man. The resources on both sides are formidable. The result is an antibiotic race which is certainly advantageous to the antibiotic manufacturers. The three synergistic weapons of the bacteria are their universal presence, their genetic variability[19,20] and their incredible growth rates. Common gram-positive and gram-negative bacteria can replicate as rapidly as every 20 minutes in standard media *in vitro*. This means that in 12 hours a single bacterium could produce 10^{11} progeny!

Physicians tend to treat defined infections and most often use "broad spectrum" antibiotics; not infrequently two or even three at the same time. Although each is chosen for a specific "coverage," nonetheless all have wide spectra. Hence, with such treatment, almost all of the hundreds of billions of bacteria which constitute the normal flora of that patient—dozens of species—are subjected to selection for resistance to each of the antibiotics. Medicine uses many foreign body devices which in themselves turn normal flora into pathogens. Increasing resistance develops in certain bacterial groups. A manufacturer introduces a new antibiotic highly active against these resistant organisms. Sales soar due to extensive use which occurs despite attempts to restrict use. Since resistant strains grow more slowly, they are also less susceptible to bacteriolytic antibiotics, thereby often requiring longer to clear. This increases the number of mutants to the new drug. A prime example of such indolent growth was that of a vancomycin resistant *S. epidermidis,* growing intraperitoneally, which persisted for 14 weeks! without either killing the patient or disappearing.[18]

A *Modus vivendi*—Is It Possible?

While "classical" bacterial infections still exist and are treated effectively with antibiotics, most bacterial infections seen in hospitals today are produced by common bacteria which were infrequent opportunistic pathogens when antibiotic use began half-century ago. When a classical contagious bacterial disease is under treatment, the objective is to eradicate the alien invader. But if that bacterium is part of the host's common normal flora, it can only be eliminated on a transient basis and then from "abnormal" sites where it normally does not grow. From the preceding sections and other sources, we develop the following principles regarding bacterial resistance to antibiotics:

1. The normal flora in a healthy individual represents a stable but dynamic equilibrium and should be altered as little as possible.
2. The indigenous antibiotic resistances of the normal flora are their most stable form.
3. Foreign bodies of all kinds increase the invasive potential of normal flora.
4. Contact between a specific antibiotic and a sensitive population of bacterial cells will promote proliferation of those bacterial cells resistant to the antibiotic.
5. Such induced resistant strains will tend to regain their native sensitivities if left unexposed to antibiotics over several generations.
6. The dosage of an antibiotic and its length of use will directly correlate with selection of resistant strains of bacteria which are *not* the target strain of the treatment program. (E.g.: A patient has a symptomatic urinary tract infection and the organism and sensitivities are known. Dosage with an appropriate antibiotic could vary from 500 mg every 12 hours for five days to 1 g every eight hours for ten days. For this and other situations, the higher dosage schedule would make it less likely that the targeted bacterium would develop resistance and more likely that the infection would be completely cleared. But that same higher dosage and longer time would produce a larger antibiotic gradient and longer time of exposure to *every* bacterium in his body, wherever located.)

7. In the hospital setting, antibiotics are not given only to the patient. The greater the use, the greater the distribution of antibiotics throughout the unit at low levels to staff and other patients by air and hand spread.

From these principles, one may formulate principles of antibiotic use designed to diminish emergence of antibiotic resistance:

1. Do not use antibiotics at all unless the need is clear. This has too many aspects to discuss here. A main point is that a "positive" bacterial culture, *per se,* is not an indication to administer antibiotics.
2. Foreign bodies should be used as sparingly as possible and removed as soon as possible. This includes simple devices used to give intravenous fluids and urinary catheters.
3. When antibiotics are used, it must be realized that multiple antibiotics, high dosages and long courses are the most effective way to increase resistant strains of all types.
4. Adherence to good handwashing practices and to standard aseptic technics to prevent spread of resistant strains is extremely important.
5. Unless restricted antibiotics are really tightly restricted, a major purpose of restriction, i.e., to keep them highly effective, will always be lost.

Conclusions

In this article, the major emphasis has been on the development of resistance by the normal flora to antibiotics. Antibiotics have indeed been a great boon. However, their continued effectiveness will depend heavily upon more judicious usage.

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Dental Developments Over the Past Fifty Years Which Affect the Geriatric Patient

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ABSTRACT

In the past half-century dentistry has changed from a narrow emphasis on the mechanics of restoration of the dentition to the interrelationship between medical problems and oral health. At the same time, the demographic imperatives of an aging population have given rise to a new subdiscipline of the profession—geriatric dentistry, which may be defined as oral health care for elderly persons, usually with multiple medical disorders, polypharmaceutical regimens, and/or psychosocial problems which render them more vulnerable to dental intervention. This chapter will explore the impact of medical developments since World War II on the clinical management of geriatric dental patients. Concomitantly it will describe refinements in our understanding of the normal and pathological effects of aging on the hard and soft tissues of the mouth. New technology with special implications for geriatric oral rehabilitation, and which are relevant to total health care, will be delineated. All of these factors have produced significant changes in the epidemiology of dental disease in the elderly and have given us new insights into the maintenance and preservation of the oral health of the elderly.

Introduction

Although dentists have always treated older patients, qualitative and quantitative changes in the past half century have resulted in the emergence of a new subdiscipline of the profession—geriatric dentistry. This may be defined as the delivery of oral health services to elderly patients, usually with at least one major chronic disorder, frequently on polypharmaceutical regimens, and

often with psychosocial problems, all of which render them more vulnerable to stress in the environment.

With some exceptions the life span of patients with major diseases which influence dental care has been increased, primarily because of effective medical treatment. Thus, although degenerative disease of the cardiovascular system is still the number one cause of death in the elderly (40% of all deaths beyond 55 years), there has been a dramatic reduction in fatalities due to ischemic heart disease in the past two decades. This is true for both sexes and for whites and nonwhites over 65 years of age, and is demonstrated by the fact that for white males in the 65–74 year cohort the mortality rate has fallen from 2119 per 100,000 individuals in 1968 to 1642 per 100,000 in 1977.[1] This decline in cardiovascular mortality is attributed to changes in lifestyle as well as newer pharmacologic agents and surgical interventions.[2] This trend, of course, is good news to potential victims of heart disease, but it also increases the number of elderly patients at higher risk for dental treatment because of pre-existing cardiac deficits and valvular heart prostheses who will require antimicrobial prophylaxis prior to invasive procedures.

The Changing Epidemiology of Dental Disorders

A dramatic change in the oral health status of the U.S. population in the past fifty years is demonstrated in a definitive epidemiological study reported by the National Institute of Dental Research (NIDR) in 1986. It must be contrasted with the fact that in the early 1940's, ten percent of potential recruits for the army in World War II were rejected because they could not meet the requirement that they must have at least six opposing natural teeth in occlusion. The NIDR study, entitled, "The National Survey of Oral Health in U.S. Employed Adults and Seniors: 1985–1986," reported on the dental status of 21,000 adults ranging in age from 18 to 103 years—this sample being statistically significant for 105 million people. It revealed an almost complete absence of edentulism (the loss of all teeth) in persons less than 40 years of age. Additional findings were that only 4% of working adults under 65 years of age were completely edentulous, and half of them had lost at most a single tooth. This is indeed a tangible reflection of the benefits of dental research in the prevention of dental disease and clinical practice in the past half century.

The survey, however, did not paint the same optimistic picture for many older Americans who grew up before World War II and did not benefit from programs of prevention. The 1985 study compared 16,000 working adults under 65 years of age with 5,000 older patients in senior citizen centers and other ambulatory elder care agencies. In the latter group, 42% are still edentulous, a disturbing fact despite a reduction of 10% from previous studies conducted in the early 1970's. And although both groups demonstrate coronal decay, i.e., occlusal or interproximal lesions, the older age group has three times a higher incidence of cervical caries—decay occurring at the junction of the crown and the gingiva (also called root surface caries) than the younger group. Both groups showed a significant prevalance of periodontal disease—

inflammatory processes of the gingiva and supporting structures of the teeth, with increasing severity in the older age group. Parenthetically, another NIDR survey of children's oral health in 1986–1987 brought the good news of a dramatic decline in the caries rate in school children aged 5–17, a further sign that Americans, in general, are experiencing better dental health than did their predecessors in the first half of this century.[3]

Much of the progress reflected in these epidemiological statistics is a result of the changing focus in dental science from a narrow emphasis on the mechanical restoration of carious lesions and treatment of gum disease to a broad understanding of the interrelationship between oral disease and the total health status of the patient. While this is true for individuals of any age, it is particularly applicable to the elderly, who are more vulnerable to pathological effects of aging on the hard and soft tissues of the mouth, as well as normal age-related changes which result in regressive physiological decrements in function. Research in aging in the past 40 years, furthermore has given us a new understanding of the impact of immunity and endocrine gland function on the oral tissues, and the reciprocal relationship between oral health and systemic disorders common in the elderly.

Salivary Function

Salivary function is too often ignored or underestimated as a factor in health and comfort particularly in older people. On a cellular and tissue level it involves the parotid, submandibular, and sublingual glands, as well as acinar glands in the palatal and pharyngeal mucosa. Whole saliva and its enzymes play essential roles in the following respects:

—a necessary lubricant for the mastication and swallowing of food
—a diluent for the taste sensations of sweet, bitter, salt, and sour
—comfort or discomfort, depending on the degree of dysfunction
—a natural detergent mechanism for the prevention of decay
—in remineralization of incipient carious lesions
—a liquid film essential for the retention of dentures

Xerostomia, dry mouth, impacts on all of these functions in varying degrees, and results from four possible etiological factors: 1) anticholinergic medications, 2) chemotherapy, 3) radiation, 4) benign and malignant obstructions of the salivary ducts. It has been estimated that 80–90% of drugs prescribed for the elderly may have a xerostomic side effect.

We have recently refined our knowledge about the effects of aging on salivary flow based on the results of a study of this oral function in the Baltimore VA Longitudinal Aging Investigation.[4] This study concluded that in a large group of healthy, aging male veterans there was no significant reduction in the quantity of salivary production. The universal application of this conclusion, however, is difficult to accept, for two reasons: 1) the study excluded females, who are certainly more numerous and typical of the geriatric population, and 2) 81% of those over 65 years of age have at least one major

chronic disorder, and a huge number of drugs consumed by the elderly have known xerostomic (i.e., mouth-drying) side effects. In our experience, the loss of intracellular water previously alluded to is implemented by the xerostomic side effects to produce varying degrees of diminution of saliva and mucous.[5]

The diagnosis of xerostomia is essentially made on a clinical base. There are some sophisticated laboratory tests which can be utilized to confirm the diagnosis, but these are usually employed to verify suspicion of an underlying systemic disorder, such as Sjögren disease. When the physician or dentist establishes a positive diagnosis, however, it is incumbent on the professional to alert the patient and prescribe appropriate therapy, as follows:

—increase intake of water in the diet, e.g. soups
—change drugs to those with least anticholinergic side effects
—counsel patient in oral hygiene procedures, including fluoride dentifrices, fluoridated mouth washes, and topical fluoride gels. This is best accomplished by the dental professional
—artificial saliva substitutes. These are now commercially manufactured and available as over-the-counter items
—in extreme cases pilocarpine has been shown to oppose anticholinergic drug effects and may be prescribed in slow-release capsule form. This drug has possible adverse side effects when the patient is taking certain drugs
—a 10 percent mixture of glycerin in distilled water, to be used as a mouth wash.

Salivary gland dysfunction can result in significant morbidity and should not be casually dismissed as a normal age-caused event. It should be carefully evaluated and vigorously treated by the physician and/or the dentist.

Burning-mouth syndrome is a pathologic entity well recognized by oral pathologists and frequently defies treatment. It occurs most commonly in postmenopausal females and is considered to have a strong psychogenic component in addition to causing glossodynia and glossopyrexia. Other etiologic factors that have been implicated include estrogen imbalance, xerostomia, iron deficiency, and malnutrition. The chief complaint is pain, either of the tongue or in a more generalized pattern. The differential diagnosis should rule out vitamin deficiency, (particularly B_{12}), iron deficiency anemia, pernicious anemia, Sjögren syndrome, Mikulicz disease, and Plummer-Vinson syndrome. Depression can also be a contributory factor, with the mouth as a focus of somatization of a depressed mental affect.

Treatment consists first in the elimination of frank pathologic factors such as concomitant lichen planus or candidiasis. Palliative agents include the use of an artifiical saliva, now available as an over-the-counter oral rinse; a mouthwash consisting of equal parts of elixir of Benadryl® with Kaopectate®, with instructions to expectorate after swishing over the tissues for one minute every

four hours and, for recalcitrant cases, 2% viscous xylocaine applied topically every four hours.

The Impact of Oral Health on the Management of Geriatric Patients

The past fifty years have taught us that the impact of oral health on the clinical management of geriatric patients can seriously compromise progress and alter prognosis. Thus, poor masticatory function may thwart efforts to provide nutritional support for the victim of a stroke, while noncompliance with recommendations for antibiotic prophylaxis of the cardiac patient has been identified as the chief etiologic factor in subacute bacterial endocarditis following dental intervention. Because the vast majority of geriatric patients have at least one major chronic disorder, the medical-dental interactions in their care by both physicians and dentists demand scrupulous attention to the effects of aging on oral function. As ever-increasing numbers of elderly are integrated into dental practice, the physician will be called on more frequently for advice on such diverse aspects of care as the drug profile of the patient and possible contraindications for certain dental procedures; the use of sedative agents to minimize stress or manage the patients with depression or dementia, and management of the patient with iatrogenic oral manifestations.

Lessons from the research in the past two decades into dental diseases in the elderly demonstrate many common denominators between medical and oral conditions. The major medical-dental interactions in the compromised older patient are described in Table I, as follows:

Table 1. Medical-Dental Interactions in the Elderly

Medical Conditions	Symptoms	Dental Aspects	Medical-Dental Interactions
Cardiovascular disorders	Dyspnea; cyanosis; edema of extremities; tachycardia; bradycardia; fatigue; nausea; vomiting; anxiety; syncope; thromboses.	Minimize apprehension and stress; avoid postural hypotension; short appointments preferable; defer elective treatment for 6 months following acute myocardial infarction.	Consult with doctor regarding antibiotic prophylaxis, sedatives, potentiated rauwolfia alkaloids, phenothiazines, and antihypertensive drugs; epinephrine contraindicated in patients receiving monoamine oxidase (MAO) inhibitors; long-term digitalis therapy makes patient prone to nausea and vomiting; observe American Heart Association recommendations for standard and special regimens.*
Hypertension	*Malignant:* seizures; retinal hemorrhages; papilledema; proteinuria and renal failure. *Essential:* Tachycardia; increased cardiac output; headache; sweating; nausea; anxiety; glycosuria; left ventricular failure; atheroma.	Patients are prone to stress and anxiety; for diastolic pressure over 110 do elective procedures only; can tolerate elevation of pressure better than depression; avoid postural hypotension; excessive post-surgical bleeding possible.	For patients on reserpine MAO inhibitors used α-stimulators (e.g., Neo-Cobefrin) rather than epinephrine; barbiturates increase CNS pressure; depression may be secondary to neuroleptics; xerostomia a side effect of drugs such as methyldopa.

Table 1. (*Continued*)

Medical Conditions	Symptoms	Dental Aspects	Medical-Dental Interactions
Cerebrovascular accident (CVA)	*Carotid* (anterior circulation): contralateral weakness, dysphasia, apraxia, and confusion, with dominant hemisphere involvement; transient ipsilateral monocular blindness; homonymous visual field defects; ipsilateral throbbing headache. *Vertebral-basilar* (posterior circulation): dysarthria and dysphagia; vertigo, tinnitus, and deafness; unilateral or bilateral sensory-motor defects; general imbalance with unilateral limb ataxia; visual field defects.	Circumoral and neuromuscular imbalance; dysphasia; aphasia; adverse effect on dentures; drooling; flexion of the neck causes management problems; hemiparesis leads to poor oral hygiene.	Anticoagulant therapy increases clotting time, affecting oral surgery; patients are prone to stress; monitor epinephrine in local anesthetics; Demerol (meperidine) increases intracranial pressure; monitor PT and PTT prior to invasive dental procedures if patient is on anticoagulants.
Diabetes mellitus	Glycosuria, polyuria, polydipsia; retinopathy; peripheral vascular changes; periodontal disease; ketosis and hyperglycemia ("brittle" diabetic).	Periodontal disease; lowered resistance to infection; delayed healing; prone to stress; prone to irritations (as with dentures); schedule patient in AM following usual insulin dose for routine care.	Consult with dentist regarding dose and type of insulin; corticosteroids can cause hyperglycemia; suggest antibiotic prophylaxis prior to oral surgery for "brittle" diabetic.
Parkinsonism	Involuntary tremors; progressive rigidity of extremities; "cog-wheel" effect; masklike facies; dysphasia, ptyalism.	Bruxism; tongue thrust drooling; slurred speech; problems in deglutition and swallowing; stress increases symptoms.	Use of epinephrine in anesthetic agents may increase stress; extrapyramidal reactions to L-dopa lead to orofacial dyskinesia; atropine causes increases in L-dopa effect.
Osteoporosis	Loss of 40% of mineral content of bone; loss of bony matrix, thin cortex, and large medullary canals in x-rays.	Loss of alveolar bone and loss of teeth have been suggested.	Potential benefits of fluoride supplementation.
Paget's disease	Acromegaly: "woolly" appearance of bone in skull x-rays; high serum alkaline phosphatase.	Progressive enlargement of maxilla and mandible; "flaring" of teeth; dentures become unstable.	
Sjögren's syndrome	Keratoconjunctivitis sicca; parotitis; buccopharyngolaryngitis sicca; arthritis; xerostomia.	Xerostomia; glosspyrexia ("burning mouth" syndrome); increased incidence of cervical caries; dysgeusia.	Patients often require psychotherapy in additon to palliative treatment; if on steroids will be more prone to stress, periodontal disease, and delayed healing.

*Recommendations of the American Heart Association, Circulation, July, 1984.
From: Kamen, S: Current concepts in geriatric dentistry. In (Levine et al, eds. Current Treatment in Dental Practice. W. B. Saunder Co. 1986), p. 394.

Inplantology in Geriatric Dentistry

A major advance in the management of the atrophic mandible, a crippling problem in the prosthetic rehabilitation of elderly patients, is the new technology of ridge augmentation inspired by developments in orthopedic surgery in the past 20 years. Three methods have now been employed by oral surgeons with varying degrees of success. The introduction of titanium subperiosteal implants since the mid 1960's was a great stride forward in meeting the challenge of the severely resorbed dental arch, but may be contraindicated in

patients with systemic disorders such as diabetes. A more recent innovation is the use of hydroxylapatite, an artificial bony material which has been employed along with hip grafts to reconstruct the alveolar ridge. Most promising however, is the result of a splendid collaboration between the Swedish orthopedist, Per-Ingvar Brannemark, and American oral surgeons in the development of the osseo-integrated implant, a precisely engineered titanium implant which is biocompatible with bone and has an excellent track record of success for the past 20 years. This striking development is a testimonial to a scientific accomplishment which is particularly beneficial to edentulous geriatric patients.

One of the more recent developments in implantology particularly appropriate for relatively healthy elderly patients is the use of surgical alloys (titanium, titanium alloy and cobalt-chrome molybdenum alloy) coated with a biocompatible hydroxylapatite (HA). This material has a strong degree of adherence to the underlying metal over an extended period of time, and has attractive properties for applications in prosthodontic and orthopedic dentistry. This has been demonstrated in both animals and humans to be a viable materials system for biological fixation because the osteophyilic type surface of the HA increases the rate of bony adaptation.[6,7] In humans, a three year clinical follow-up of four hundred fifty seven HA coated implants placed in 130 patients for prosthetic restorations noted that osseous biointegration was achieved in as early as eight weeks.[8]

One of the promising developments in periodontal and prosthodontic rehabilitation is the utilization of a new polymer called HTR (hard tissue replacement) as a synthetic bone substitute. This material is a nonresorbable, microporous, synthetic bone grafting agent that combines a polymethylmethylacrylate core with a polyhydroxylethylmethacralate (polyhema) coating which produces a biocompatible composite without the addition of catalyst inducers or impurities. This HTR polymer is premixed and packaged in a sterile unit ready to use.[9] The material has been employed in periodontal surgery where it has proven successful in the repair of osseous deficits and intrabony pockets, and in alveolar ridge reconstruction, in which it acts as a vehicle for a bone-inductive substance that remodels the mandible by converting connective tissue to alveolar bone.[10,11]

Kamen has conducted histological in vitro studies which demonstrate the kinetics and morphology of the attachment of human gingival fibroblasts to HTR® polymer. Although he cautions against the interpolation of in vitro findings to in vivo situations, he is quite optimistic that this material augments connective tissue repair, promotes wound healing, and will be a valuable addition to the armamentarium of periodontal and prosthodontic rehabilitation.[12]

A major consideration in implantology, which has not as yet been adequately addressed, is the feasibility of the use of these new materials in geriatric patients with various disorders, and particularly the interface of artificial bone substitutes with osseous tissue in patients with osteoporosis.

Oral Rehabilitation

In the early 1970's the use of polymethylmethylacrylate resins as an esthetic material for the repair of carious lesions was dramatically enhanced by the technique of acid etching of the enamel surface.[13] The teeth are cleaned with flour of pumice, isolated with a rubber dam, and an unbuffered solution of phosphoric acid is applied for one (1) minute. This procedure results in microporosities of the enamel surface which mechanically interlock with bis-GMA composite resin tags. Retention of the restorative material is aided by the use of a bonding agent—an unfilled resin of low viscosity which readily penetrates the microscopic irregularities, and then chemically bonds with a filled resin. An ultraviolet photocure unit (white light) is utilized to polymerize the resin restorative materials, and offers the clinician adequate working time for placement, contouring and polishing. Because people are living to an older age and are retaining their natural teeth these esthetic materials are constantly being perfected and are in ever increasing demand. Thus, a new resin called a glass ionomer cement which bonds to dentin has been found to be more appropriate for the common carious lesion affecting adult teeth-root surface decay. Both erosion and carious defects are now restored with the glass ionomer cements. The advantages of these materials are their esthetic and cosmetic appearance, superior retention, slow release of fluorides and protection against marginal leakage. Their durability remains to be tested in the years ahead.[14]

The therapeutic effect of fluorides on root and coronal caries in older adults has been well documented in several studies. Banting and Stamm have compared root caries prevalence in adults in fluoridated and nonfluoridated communities in Canada, and confirm a dramatic reduction in carious lesions in the fluoride protected subjects.[15] Of even greater significance in geriatric oral rehabilitation is the report of Nyvad and Fyerskov that incipient and active root surface cavities can be arrested and rendered inactive with rigorous oral hygiene utilizing fluoridated dentifrices and mouth washes.[16,17] The author routinely recommends to his geriatric patients the daily application of a stannous fluoride gel before retiring. In view of the technical difficulties in repairing root surface caries the employment of preventive measures such as these are certainly merited.

The beneficial effects of a sodium fluoride dentifrice was demonstrated in a carefully controlled study of 810 subjects 54 years of age and older who were living in 43 communities in Iowa without a fluoridated water supply. The test dentifrice contained 1,100 ppm F as sodium fluoride, compared with <1 ppm F in the control group. After one year there was a 41% reduction in coronal caries and a 67% decrease in root surface caries.[18]

The prime etiological factor in periodontal disease is the deposition of plaque, an invisible film consisting of microorganism in a substrate of mucous and carbohydrates, which results in a concatenation of events including gingivitis, gingival recession, pocket formation, i.e., loss of gingival attachment, and the loss of the supporting bony matrix of the tooth. Basic periodontal

therapy therefore, requires the elimination of infection and inflammation by controlling caries and removing plaque on the coronal and root surfaces of the teeth by scaling and root planing. Residual bony defects are then surgically treated with the synthetic bone substitute.

Treatment of the Terminal Dentition

It has been estimated that 42 percent of all individuals over 65 years of age in the U.S. are completely edentulous, i.e., have lost all of their natural teeth. Previously it was common practice to remove any remaining roots and tooth fragments prior to fabrication of dentures. This often resulted in additional atrophy and resorption of the alveolar ridges. It is now generally accepted that the retention of these remnants preserves the integrity of the maxilla and mandible, and aids in the function and stability of prosthetic appliances.[19] The methods employed to retain these roots, and sometimes to bury them beneath the alveolar mucosa, are highly technical and beyond the scope of this review, but to a great extent have revolutionized prosthodontic rehabilitation, especially for the geriatric patient. The appliances constructed over these modified roots are called overdentures, and have enormous advantages in maximizing comfort and function.[20] A sophisticated array of attachments, bars, and other devices attached to the roots further enhance the stability of the overdenture, and are increasingly being utilized by dental geriatricians. It is incumbent on the patient to practice meticulous hygiene of these appliances and the physician should reinforce the dentist's instructions towards this goal. Desjardins has stated that "successful rehabilitation must also incorporate preventive and maintenance care. To achieve a rehabilitation that cannot be maintained, and which encourages development of additional disease, defies the goals and objectives of the dental professions.[21]

Conclusions

The experience of the past several decades posits that poor oral health can have a domino effect on the total health status of the elderly patient, diminishing the quality of life and leading to metabolic imbalance, malnutrition, anorexia, and cachexia. Thus, dental disease per se can significantly influence the multiplicity of chronic illnesses that characterize the elderly, while at the same time the medical disorders complicate the dental treatment. Although today's elderly are healthier than in the past, the very fact that they are living well into their 80's and 90's means that they become more vulnerable to a variety of chronic illnesses, including cardiovascular conditions, neurologic disorders, metabolic deficiencies, Alzheimer disease, and other types of mental impairment. These elderly patients are at high risk for dental intervention, and the gerodontist will frequently consult the physician to discuss clinical management.

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Some Social, Scientific and Technologic Changes in Medicine from 1935 to the Present

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ABSTRACT

Changes in the prevention and treatment since 1935 of the major causes of death and disability in older people are discussed. Today, these major diseases are not infectious diseases but chronic degenerative diseases and cancer. For individual patients, there have been major improvements in several areas. Yet for society as a whole, the prevalence of these diseases has greatly increased.

In the preceding article, we discussed antibiotics as the single most important medical advance since 1935. In this article, we will address some of the many other changes which have occurred. For non-medical readers, a few definitions are required. The "mortality rate" refers to the number of deaths due to a certain cause per 100,000 population per year. When comparisons are made where the demography may vary, it is necessary to correct for age. For example, both heart disease and cancer are strongly correlated with age. In 1935, the average age of the U.S. population was considerably younger than in 1985. Uncorrected mortality rates for these diseases would therefore show marked increases in 1985 compared with 1935 solely on the basis of the demographic change. "Morbidity" refers to illness from a disease or other cause. "Incidence" means the number of cases recorded for the first time during a given year while "prevalence" refers to the number of people ill with a given disease during a year span. If a person developed chronic heart disease in 1965 and died from it in 1985, he would be counted in the "incidence" statistics for 1965, in the "prevalence" statistics in each of the 20 years. He would be recorded also in the morbidity statistics for each year and in the mortality statistics for 1985.

The diseases discussed represent the major causes of death and disability in 1985. Hence, many well-known diseases are not discussed or even mentioned; this does not imply that important new treatment methods have not emerged for them over the half-century.

Tobacco Usage

From a medical viewpoint, the most important social change since 1935 has been the shift in public support for smoking cigarettes. In America, this habit became prominent among the military during World War I. It spread rapidly among men and more slowly among women and by the early 1950s over 60% of men were smokers. But in 1939, Oschner, an American thoracic surgeon, reported that most of the patients with lung cancer which he saw were heavy smokers of cigarettes. By 1964, enough data had accumulated on the multiple adverse health effects of smoking for the Surgeon General of the Public Health Service to issue his now famous first report on "Smoking and Health." Smoking is far and away the most important preventable cause of serious disease in the United States. In 1985, the overall mortality rate was 874 per 100,000 population. Of this total, 130 are estimated to be due to tobacco use. The range by states is from 176 in the prominent tobacco state of Kentucky to a low of 45 in the state of Utah with its large population of non-smoking Mormans. Of the many effects of smoking,the most prominent are lung damage. Almost every patient developing lung cancer receives extensive treatment with all the types of treatment which offer any hope—surgery, radiation, chemotherapy with multiple drugs. Despite such intensive, high technology treatments, five years after diagnosis 87% of lung cancer patients are dead. Lung cancer usually develops in patients with chronic obstructive lung disease (COPD), which includes emphysema and is almost totally due to smoking. The morbidity for this disease is extreme and goes on for years. Development of more effective broncho dilating drugs and antibiotics and the extensive home use of oxygen as compressed oxygen or as oxygen concentrators of room air has ameliorated the symptoms of COPD without reversing the pathology. The only bright light in this bleak picture is that since about 1955 there has been a gradual decrease in cigarette use which from 1974 through 1985 has been an almost linear decline. The 1985 smoking rates for men was 33.5% and for women 27.6%. Soon women will outnumber men as smokers. People aged 65 in 1985 would have been age 35 in 1955 so their smoking patterns were well-established long before the dangers of tobacco to health became defined. However, many of the effects are reversible and a great many of this age cohort and older have stopped. This change in smoking patterns must rank second to antibiotic development as a major determinant of the health of the older patient.

Heart Disease

Diseases of the heart lead the list of causes of death producing over a third of all deaths in 1985. In 1935, rheumatic heart disease and syphilitic heart disease were frequent causes of death but they have been vanquished by

penicillin and today coronary artery disease is the dominant cause with atherosclerosis being the underlying pathology. The past 50 years have seen advances in the treatment or prevention of heart disease from multiple approaches: Prevention, medical treatments, surgical treatments, even after-death treatments with cardiac resuscitation! Prevention has focused on three approaches: Decrease in smoking, decrease in cholesterol and fat intake and an increase in exercise. In our frequently lethargic society, it is very encouraging that every one of these has shown marked improvement at the society level, even though many persons have not changed their patterns at all. We now have more effective and less toxic drugs to reduce cholesterol and/or lipid levels if dietary changes are insufficient.

Coronary Artery Disease

Atherosclerosis causes mortality and morbidity through myocardial infarctions, cardiac arrhythmias, congestive heart failure and angina pectoris. In the preceding paragraph we noted preventive measures relating to smoking, exercise and types of foods. Another preventive measure is the use of aspirin in low dose to prevent repeated heart attacks by decreasing platelet agglutination. Diabetes is another risk factor for atherosclerosis and better diabetic control has helped.

Surgical treatment of heart disease (open heart surgery) has had superb media coverage and coronary by-pass grafts using vein grafts from the patient (CABG) has had great success in relieving symptoms, especially angina, and lesser success in prolonging life. While heart transplants are no longer a rare surgical procedure, there are many complications and they have little impact on the overall picture. Mechanical hearts are entirely experimental and will remain so for a long time.

The drama of cardiac surgery has tended to obscure the amazing advances in the drug treatments of heart disease over the half-century. In 1935, the powdered leaf of the foxglove, which contained digitalis, was still the most commonly used medication. The purified glycosides, digitoxin and the shorter acting digoxin, were purified in 1925 and 1930 respectively but were not widely used for about 20 years. Digitalis had been introduced in the treatment of congestive heart failure (dropsy) by William Withering in 1785. When I was in medical school in the mid-1940s, I was taught that digitalis, unlike most drugs, had an "all or none" effect. This meant that blood levels just below toxic were required and indicated use of the long acting digitoxin to keep the level more constant. There was no assay method for serum digitoxin then available, nor was hemodialysis available. As a result, digitoxin toxicity was rather frequent, especially in older people. When radioisotopes became available, the development of radioimmunoassay methods became possible. This was particularly valuable for measuring substances such as digitoxin which have very low serum concentrations. Using this technic, it was soon demonstrated that digitalis preparations behaved just like other drugs; they did not have an "all or none" pattern but the usual dose-response effect. This led quickly to dropping digitoxin and using digoxin, the shorter-acting and there-

fore safer drug. This story illustrates what the results can be when well-established principles appear inconsistent with clinical experience and the clinical results are used to justify the practice. In the mid-1940s, the principle in pharmacology of a dose-response curve was well-established. Both the glycosides were then available, but the more toxic was deliberately selected based on inadequately controlled clinical studies. After 200 years, the digitalis glycosides remain the best cardiotonic drugs but the safety of their use has greatly increased. Digitalis is also less needed than in 1935 because of new drugs with different actions which are also needed in the treatment of congestive heart failure (CHF). The most important are the oral diuretics.

In 1935, there were no good diuretics for chronic use; the mercurial diuretics were effective but required injection and were often toxic if renal insufficiency was present. In the early 1950s, when penicillin was still expensive, one of the pharmaceutical companies set out to find a drug which would decrease the renal tubular secretion of penicillin and therefore maintain higher serum levels. A chemical which did this effectively in man was found (probenecid), but very shortly the price of penicillin fell steeply, making the product of less value. However, probenecid also increased uric acid loss so was useful in the treatment of gout and the company decided to continue its renal program. One of the chemicals synthesized for the program was found to have marked diuretic and hypotensive effects. This was chlorothiazide, the first of the effective oral diuretics and still today, as hydrochlorothiazide, a very useful drug in treating both congestive heart failure and hypertension. However, the type of diuretic most often used today in treating CHF is a "loop" diuretic, such as furosemide. These drugs very effectively reduce the reabsorption of sodium and chloride in the renal loop of Henle.

Angina Pectoris

This is the most frequent cause of chronic disability in patients with coronary artery disease. Since pain is the symptom which most often causes people to visit doctors, angina causes many office visits. Yet in 1935, the only really useful drug was sublingual nitroglycerin. Synthesized in 1846, its medical use began over a century ago. The very major effect of nitroglycerin on the history of science began in 1862 when Alfred Nobel patented dynamite, which incorporates nitroglycerin with diatomaceous earth and a small amount of sodium carbonate. In a very real sense, nitroglycerin was the founder of the Nobel Prizes! Although sublingual nitroglycerin is very effective in the prevention and treatment of acute anginal attacks, it is very short-acting. Much effort has been made to prepare oral nitrates which could be used on a continuing basis to prevent anginal attacks. Several preparations have been used extensively but have not been highly effective. Today we use nitrates delivered through the skin rather than orally. However, we also have other effective anti-anginal drugs. The β-adrenergic blocking agent propranolol was the first of these. This drug has almost the reverse effect of digitalis in that it decreases the force of cardiac contraction. The cause of pain in coronary artery disease is oxygen lack, produced when the ratio of oxygen demand to oxygen supply

is too low. Propranolol, by decreasing myocardial contraction, decreases oxygen demand and hence decreases anginal attacks. The effect lasts for several hours and newer preparations are effective for even longer periods. Just when the "beta blockers" were well established, a whole new group of cardiac regulating drugs appeared: The calcium channel blocking agents. The biochemistry of muscle contraction requires that the calcium concentration inside the muscle fiber be increased. Calcium ions enter the fiber through tiny channels. These new drugs, e.g., nifedipine, diltiazem, verapamil, inhibit this Ca^{++} increase, thereby decreasing contractility with decreased oxygen demand. Using combinations of old and new cardiac drugs, many patients with coronary artery disease can be treated as effectively medically as surgically. There is now enough data to separate fairly well those patients who will do well on a medical regime from those who will benefit more from a coronary artery by-pass procedure.

Hypertension

Although hypertension is found in all ages, it is most frequent over age 65 with about one third of all people in the U.S. over 65 having some degree of hypertension. The most important sequellae are congestive heart failure and strokes, although many cases of kidney failure are also due to long-standing hypertension. In 1935, there was *no* satisfactory drug treatment. It was not until almost 25 years later that the effective combination of a thiazide diuretic coupled with a specific anti-hypertensive drug such as methyldopa became available. Today there are almost too many antihypertensive medications! The reason there are so many is two-fold. Some patients have very resistant hypertension so are on multiple drugs and even then may not be controlled. The "ideal" drug for hypertension is one of the hardest assignments possible for the drug industry. None of the medications "cure" hypertension so long-term treatment is the norm, even though remissions occur. But high blood pressure itself causes symptoms in only a small fraction of all people with hypertension. Therefore, for most Americans under treatment for hypertension, the "symptoms" of their disease are actually the side effects of the antihypertensive drugs. This makes long-term compliance extremely difficult. So the quest continues for an oral drug, taken once or twice daily, that will have almost no side effects. Despite all these problems, the treatment has vastly improved since 1935 and is being used by millions of patients. It has decreased mortality rates from strokes and congestive heart failure.

The most specific, and therefore one of the least toxic, antihypertensive agents are the angiotensin-converting enzyme (ACE) inhibitors. The background for these goes back over half a century. In 1934, Goldblatt showed that chronic renal ischemia would produce persistent hypertension. He felt that both experimental and clinical hypertension were produced by increased secretion of a renal enzyme, renin. He tried to inhibit renin but could not develop a suitable method. While the "Goldblatt kidney" remained a standard method of producing experimental hypertension, anti-renin studies were not pursued. Many years passed before the renin-angiotensin-aldosterone system was worked out. Briefly stated, renin acts on a serum globulin to produce a

decapeptide, angiotensin I, which is not active. A serum enzyme converts the decapeptide to an octapeptide, angiotensin II, which is a potent vasoconstrictor thereby raising blood pressure. Angiotensin II also stimulates the adrenal gland to secrete the mineral-corticoid hormone aldosterone which increases blood volume and enhances the hypertensive state. One way to block the effects of increased renin would be by blocking the conversion of angiotensin I to angiotensin II. Some snake venoms contain toxic peptides which may produce shock. In 1965, Ferreira isolated a mixture of peptides from the venom of a Brazilian snake, and in 1967, Ng and Vane found that one of these peptides blocked conversion of angiotensin I to angiotensin II. By 1971, Ondetti et al had synthesized the nonapeptide. Laragh and his colleagues demonstrated that the peptide did, indeed, decrease blood pressure in patients with elevated renin levels. However, it required intravenous injection so had minimal market potential. Hence Cushman and Ondetti set about developing a peptide-like product that would be an ACE inhibitor when taken orally. This they achieved and captopril was patented in 1977. A decade later we have even more specific ACE inhibitors. Furthermore, they are often effective even when renin levels are low, which somewhat confuses the tidy theoretical development of these important drugs.

Cardiovascular Disease Today

In the preceding pages we have presented the many ways in which we have improved the prevention and treatment of cardiovascular diseases. In the 1950s, a longitudinal study of cardiovascular diseases was set up in Framingham, Mass. This is known as the Framingham Study and many people, originally without any evidence of cardiovascular disease, have been followed until death or for over 30 years. Over these 30 years, there has indeed been a fall in the cardiovascular mortality rate of the study population as has also occurred nationally. But there has been no decline in the incidence of cardiovascular disease. Hence, we have not yet reached either true prevention or cure with these many advances, but have made the diseases milder. If the mortality rate has fallen but the incidence has not, it must follow that the prevalence of cardiovascular disease has actually increased.

Cancer

Cancer was the second largest cause of death in both 1935 and 1985. However, instead of declining, the overall rate almost doubled. The most spectacular change was for lung cancer in men, climbing from 7 in 1935 to 74 in 1985. In a reverse trend, stomach cancer fell from 38 to 9. In women, these values were from 3 to 27 and 28 to 4 for lung and stomach respectively. In men, cancer of the colon and rectum and of the prostate rose slightly between 1935 and 1945, then leveled off and have remained between 20 and 30 ever since. Women showed the same initial rise in colon and rectal cancer as men but this has fallen from a high of 27 in 1947 to 18 in 1985. Uterine cancer (cervical and endometrial) has fallen from 30 in 1935 to 7 in 1985. Breast cancer, the most frequent cause of cancer deaths in women from 1933 to 1988

(when overtaken by lung cancer), has shown no meaningful change, being 27 in 1935 and 28 in 1985 with only minor variations during the half-century between. Hence at the statistical level of mortality rates, the only good news for the major types of carcinoma is for cancer of the stomach and uterus. Results have been somewhat better for the leukemia/lymphoma malignancies, especially for Hodgkins Disease where a significant percentage of true cures have been achieved with aggressive radiation therapy and/or chemotherapy.

Five-year survival rates have shown modest improvement for the major cancers. Data covering the 1960–1984 period show the percentage of cancer patients surviving five years rising from 39 to 50% for all types of cancer (for whites). Colon cancer rose from 43 to 53%, lung cancer from 8 to 13%, breast cancer from 63 to 75%, prostate cancer from 50 to 73%. Since survival time begins when the tumor was diagnosed, these figures measure improved diagnostic methods at least as much as improved treatment.

Huge amounts of resources have been put into cancer research and treatment and we know much more about carcinogenesis at the cellular level than in 1935. Yet we understand little about cancer in man and, overall, treatments have made little progress. The development of genetic engineering has made the production of such natural products as interferon possible but interferon has had only limited success in cancer treatment. Demographic studies show large differences in cancer incidence by country. For example, breast cancer is almost six times as frequent in England and Wales as in Japan and prostate cancer is five times as frequent in the U.S. as in Japan. Yet stomach cancer is almost eight times as frequent in Japan as in the U.S. The causes of these large differences have not been determined. Difficulties in identifying causes is shown by the history of cigarette smoking as a cause of lung cancer. This year marked the 25th anniversary of the first Surgeon General's Report on Smoking and Health in 1964. It should be appreciated that the first good studies showing a correlation between lung cancer and cigarette smoking were reported in 1939 by Muller in Germany and Ochsner and DeBakey in the U.S., exactly 25 years *before* that first Surgeon General's Report. For gastrointestinal cancer, the major focus today is on dietary differences in various groups. Despite multiple theories, the major factors responsible for breast cancer and prostate cancer remain undetermined. Even when a general etiology has been established, the specific etiology can be extremely difficult to identify. Cigarette smoking has been known to cause lung cancer for 50 years and literally thousands of studies of the effects of ingredients of cigarette smoke have been made. Yet today, there is no firm evidence identifying a specific chemical compound as *the* major cause of lung cancer from cigarette smoking. Hence, we may expect that the much less well defined ingredients of "diet" will be even more difficult to unravel.

Diabetes

Insulin was first used in 1922 and crystallized in 1926 so its use in diabetics was well-established in 1935. The reported death rates for diabetes in 1935 and 1985 were not very different, but such rates cannot be accurate because

diabetes is a major risk factor for heart disease and is the chief cause of end stage renal disease. Our supportive systems are so much better that the number of deaths from ketoacidosis must be much lower. Despite this, diabetes in 1985 is a much more common disease than in 1935. Today the insulin is a true human insulin produced either by a genetically engineered bacterium or by chemical modification. Almost more amazing is how satisfactory pork and beef insulins were over a sixty-year period. Since these are foreign proteins, they did produce antibodies which at times required increases in insulin doses. But only rarely did patients become totally resistant to insulin. Foreign proteins can produce anaphylactic shock and severe kidney damage but both were rare with these foreign insulins. The reason must lie in the small differences between human, beef and pork insulins. Insulin has a molecular weight of six thousand and has A and B chains joined by disulfide linkages. Pork insulin differs from beef insulin by two amino acids sequences while pork insulin differs from human insulin by only one amino acid sequence, clearly demonstrating that humans are more closely related to pigs than to cattle! Since the difference between human and pork insulin is the C-terminal amino acid, chemical replacement of the alanine with threonine produces a human insulin. Alanine is an aliphatic amino acid with a single methyl side chain. In general, antigenicity in proteins correlates with the complexity of the amino acid side chains and aromatic radicals are much more antigenic than aliphatic radicals. Hence, only if pork insulin had a C-terminal glycine instead of alanine could it be less antigenic in man.

The antimicrobial era was introduced with the sulfonamides in 1935. Even though true antibiotics became the dominant antimicrobial drugs, work on finding better sulfonamides continued and lead to the sulfonylureas in 1957. These drugs, e.g., tolbutamide and chlorpropamide, have no antibacterial action but lower blood sugar and are effective orally. Recently 100-fold more potent oral drugs have been introduced. These oral antidiabetic drugs have been extremely useful in diabetic treatment, but have not replaced insulin for severe diabetics. In fact, insulin today is given at more frequent intervals than even a few years ago to better control fluctuations in blood glucose.

In 1935, monitoring of blood glucose at home was done by quantitative measurements of urine glucose. This method revealed pooled blood glucose levels over a previous time period but did not measure low levels at all since the renal threshhold for glucose is in the range of 180 mg%. Today, urine monitoring is little used with microamounts of blood from fingersticks providing quantitative blood glucose levels measured in simple machines. Various attempts to provide implanted insulin pumps and continuous glucose monitoring for automated insulin delivery have not yet been perfected but progress is expected.

Diabetes and its many complications remains a leading cause of death and disability. Even if automatic infusion pumps improve and become widely available, they will remain cumbersome and have problems. Research efforts on the etiology of diabetes give hope that some diabetes may be preventable. For now, the goal of the diabetic must be to follow a carefully controlled diet with appropriate drug dosage which keeps glucose levels at near normal levels but does not subject the patient to severe hypoglycemic episodes.

Arthritis

So far, we have dealt with diseases which have high mortality rates. These same diseases also produce a great deal of morbidity, i.e., discomfort or disability or both. Of those diseases which produce high morbidity rates but low mortality rates, arthritis is dominant. In a survey of people over age 65, almost half reported arthritic symptoms. The actual prevalence of arthritic changes must be even higher, since x-rays taken for other purposes frequently show severe arthritic changes in patients asymptomatic for arthritis. Arthritis is a generic term and has many varieties but two types account for most cases: Rheumatoid arthritis (RA) and osteoarthritis (OA), also known as degenerative joint disease (DJD). Although OA is far more common, RA has been the subject of much more research. This reflects both the severe crippling effects of RA and its intriguing immunological factors. Most patients with RA have a serum factor termed "rheumatoid factor" which is an antibody against denatured antibody of the IgG type. Arthritis attacks joints, but the bone itself is only secondarily affected. In OA, the primary tissue response is in cartilage, while in RA it is the synovium which lines the joint.

Soon after cortisone became available in the late 1940s, it was shown to produce dramatic improvement in certain patients severely crippled with RA. However, the side effects of chronic steroid use can be severe and improvement was often not maintained. Aspirin was widely used and was effective in RA but required continued use of large doses. Hence, pharmaceutical companies searched for a drug which would be more effective than aspirin but less toxic than steroids. The first product was indomethacin, introduced in 1962. This group of drugs carries the acronym of NSAID, for "non-steroidal anti-inflammatory drugs" and many different products with slightly different characteristics are now available. RA is a severe inflammatory disease and these drugs were developed for RA. At the time, OA was felt to be non-inflammatory, and the British therefore use the term "osteoarthosis" instead of "osteoarthritis" which does carry a connotation of inflammation. Since OA is much more common than RA, the NSAID drugs were promptly tried in OA and found to be very helpful. Following this therapeutic finding, it has been shown experimentally that inflammation is indeed an important part of OA.

Despite these drugs and others used in arthritis, both RA and OA can progress to make joints non-functional. For such patients, the major advance has been in orthopedics, with the development of total joint replacements. Particularly successful has been hip replacement which has made a great many patients crippled with arthritis once again ambulatory.

Yet arthritis remains *the* major cause of morbidity for people over age 65 and much more basic and applied research is required.

Mental Illness

Another area with high morbidity but low mortality is that of diseases affecting the brain. The original hope that psychotherapy would resolve such

functional diseases as schizophrenia and manic-depressive (bipolar affective) disorders has not been borne out and these diseases are now known to be heavily dependent upon genetic factors. Chlorpromazine was introduced in France in 1952 and this group of drugs has had a dramatic effect on the treatment of schizophrenia. Their extensive use has led to large scale discharges of schizophrenics from mental hospitals. It should be realized that the drugs do not cure the disease and rarely completely normalize the altered thought processes. Also in the early 1950s, the simple chemical lithium carbonate was shown to be effective in control of manic symptoms. A few years later an analogue of chlorpromazine was shown to be effective in depressed patients while ineffective in agitated schizophrenics. The dibenzazepine nucleus of this drug, imipramine, differs from the phenothiazine nucleus of chlorpromazine in the linkage between the two benzene rings. Imipramine and related compounds are used with good results in most cases of bipolar depressed states but are of lesser values in depressions of other types.

Non-psychotic mental illnesses vastly outnumber schizophrenia and manic-depressive disorders. Depression, anxiety, stress syndromes and substance abuse with their myriad permutations and combinations permeate our society. Primary physicians dispense huge quantities of the benzodiazepines typified by diazepam (Valium). Psychiatrists couple more judicious drug use with psychotherapy while new professional groups, e.g., clinical psychologists, use only psychotherapy to aid patients coping with these problems. Perhaps the greatest change since 1935 is the acceptance of the frequent need for professional help to resolve problems in which emotion and mood are paramount. Although there are no good statistics, it appears that there has been a major increase in depression, anxiety and stress syndromes since 1935 and there certainly has been a huge increase in substance abuse. Many cases of these disorders stem, at least in part, from our social organization, and since prevention is certainly more effective and desirable than treatment, psychotherapy and medical treatment cannot be expected to have much effect on the incidence of these problems.

In the older age group which we are primarily addressing, the most prominent mental illness is dementia. The most frequent types, Alzheimer's Disease and multi-infarct dementia, are not only untreatable but are devastating for both patient and caretaker. Multi-infarct dementia is due to strokes which are highly correlated with hypertension. Hence, we have some preventive measures for it, but not for Alzheimer's Disease. Both types of dementia are highly correlated with age so our aging society will show increasing incidence. Even more important, however, is the increase in prevalence. This is due in large part to application of all our modern technology to prolonging the lives of severely demented patients. It is very effective in that goal, which coincides with prolonging the suffering of their caretakers. Not only routine technologies but cardiac surgery, repair of asymptomatic aortic aneurysms, full treatment programs for cancer, continuing hemodialysis are applied alike to demented and undemented patients. While research in dementia must be vigorously pursued, there is no possibility that research will resolve the increasing problem of dementia in the foreseeable future.

Hearing Loss

About 30% of people over age 65 have a symptomatic degree of hearing loss. We now know that high noise levels have a cumulative effect over the years on auditory acuity and much more stringent ear protection is required in the workplace. At the same time, young people have vastly increased noise levels in their recreational activities! The chief change in hearing aids has been miniturization. Eyeglasses require only periodic changes in refractive prescription done at periods of years, while hearing aids require ongoing adjustments in the volume control. This poses a particular problem in just that population who need them most. Older people have more arthritis and less ability to make rapid and fine adjustments of those tiny volume controls. Putting in batteries and turning them on and off are major problems for millions of users. Hearing loss isolates people from other people and is a major cause of depression and withdrawal. We do not realize how often we repeat or emphasize a point in ordinary conversation. Our superb memory often reflects not such good memory but the repeated input of the item. The person who is hard of hearing has much trouble getting the message once, much less multiple times. A great many older people are thought to show senile memory loss when the real problem is only hearing loss. All hearing cannot be helped by hearing aids, but there is no question that the technology in use today is very unsatisfactory for millions of users and potential users.

Chronic Sinusitis

When a sample of the general population over age 65 was asked about chronic diseases which affected them, the top four were, in descending order of frequency, arthritis (50%), hypertension (39%), hearing impairment (30%), and heart condition (26%). The fifth most frequent, at 15%, was chronic sinusitis. This definition includes patients with chronic nasal congestion and post-nasal drip who do not show evidence of chronic sinusitis by x-ray. This entity does not produce severe morbidity for most but it is certainly uncomfortable and a nuisance. The etiology is poorly defined but allergy, low-grade bacterial infection coupled with structural features of the anterior skull which alter drainage patterns are probably important. Vasoconstrictor drugs may give transient relief but have long-term bad effects and indeed can worsen the symptoms. Antibacterial therapy can be very helpful but again only transiently. Nasal instillation of steroids can be helpful for some. Various surgical procedures have never become established as very helpful. Hence, chronic sinusitis remains an unexpected but major cause of morbidity and deserves further study.

Vision Loss

About 10% of people over age 65 have significant uncorrected vision loss. The major causes are cataracts, diabetic retinopathy and glaucoma. The treatment of cataracts has vastly improved since 1935. At that time, patients spent

two weeks in the hospital and were subsequently fitted with very thick glass lenses which at best produced distortion in size. Today the surgery is usually done on an out-patient basis and an intraocular lens implanted. Subsequent fitting of eyeglasses is no different from routine refraction. Diabetic retinopathy has been improved by laser treatment and has been very valuable for individual patients. However, there are more diabetics, they live longer and the development of retinopathy requires many years in the diabetic state. Therefore, there are many more cases of vision loss from diabetes which is today the chief cause of blindness in the United States.

Conclusions

Since 1935 there has been a tremendous increase in biomedical knowledge and many new drugs and surgical procedures have brought a better life to older patients with a wide variety of ailments. However, a viewpoint expressed by Rene Dubos should be kept in mind. In the early 1960s, the University of Kentucky opened a new medical center complete with schools in all the major health sciences and a university hospital. Dubos, an eminent microbiologist at the Rockefeller University, was the major speaker at the dedication ceremonies. To the governor, senators, officials from HEW and the university, faculty and general audience, Dubos noted that everyone in the audience expected that this new and expensive medical center would decrease the prevalence of disease in the Commonwealth of Kentucky. It would not do so, declared Dubos. All the effort would only change the pattern and mix of the diseases which presented, but would not decrease the overall prevalence of disease. Twenty-five years later, he appears to have been correct.

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