The Control of Hyptertension in the Elderly: Understanding the Challenge, Responsibility and Opportunities for Preventive Interventions in the Elderly

Ron J. Anderson, M.D.
President & Chief Executive Officer
Parkland Memorial Hospital
Associate Professor, Internal Medicine
The University of Texas Health Science
Center at Dallas

Parkland Medical Grand Rounds
-3 Part-
7/18/85

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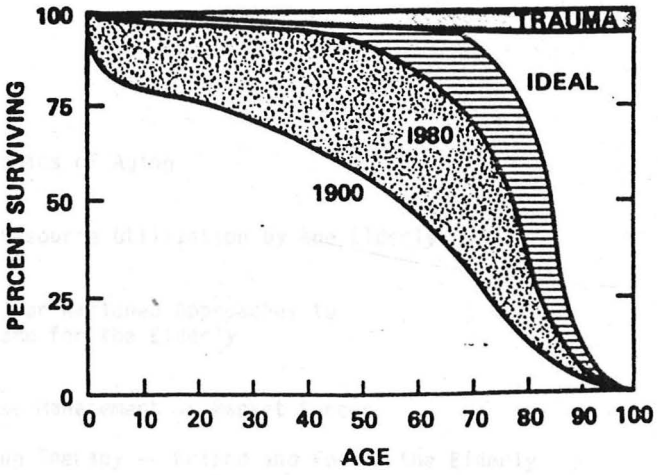
Dedication

This work is dedicated to the treasure I have personally received from elders such as my grandfather, Charles B. Harston, whose pioneer spirit and life's model have become a yardstick to measure myself against, and to the wisdom, energy and commitment of Ralph B. Rogers who helped set Parkland back on the road to greatness. The following statement by Mr. Rogers is the real essence of our challenge in caring for the elderly:

> "This is a community enterprise, owned by the people and dedicated to one class of care for all, the very best. There are no classes of society recognized by the institution, our belief in human dignity precludes it."

Facing the Challenges of Success: Healthcare in the Elderly



"May you live all the days of your life."
--Jonathan Swift (1738)

Ron J. Anderson, M.D.
President & Chief Executive Officer
Parkland Memorial Hospital
Associate Professor, Internal Medicine
The University of Texas Health Science
Center at Dallas

Part I
Parkland Medical (Economic) Grand Rounds
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Part I: Facing the Challenges of Success:
Healthcare in the Elderly

Forecasts of the age composition of the United States reveal an unprecedented and rapid increase in the size of the elderly population.(Figure 1) In 1980, the over age 65 population represented 11.2% (9.4 million) of the general U.S. census.(1) (Table 1) The over age 65 population has increased eight fold in this century compared to a three fold rise in the general population. Placed in perspective, of all the aged 65 ever living in the United States, half are living today(2) and this age group will continue to be the fastest growing segment of our population for decades to come.(Figure 2)

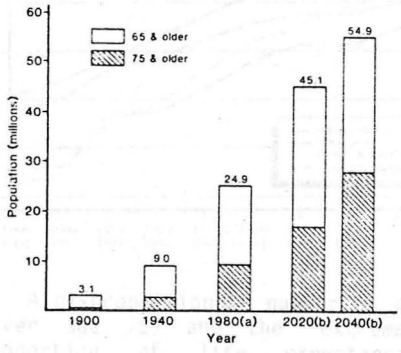


Figure 1 Growth of the older population in the United States: 1900–2040. (a) estimate. (b) projections (base date of projections is July 1, 1976). (Source: U.S. Bureau of the Census.

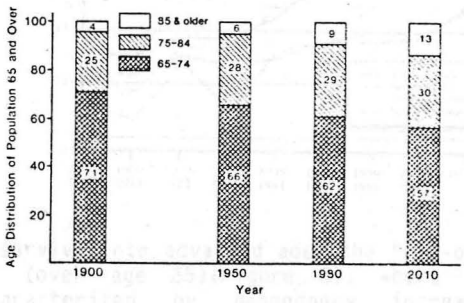


Figure 2 Percentage of the very old among the elderly population in the United States: 1900–2010 (rounded to the nearest percent). (Source: U.S. Bureau of the Census [1] and the U.S. Department of Health and Human Services, Federal Council on Aging.

Table 1 NUMBERS AND PROPORTIONS OF OLDER PEOPLE IN THE UNITED STATES: 1900–2040

Year	Number of Persons 65 and Older	Percent of Total Population 65 and Older	Number of Persons 75 and Older	Percent of Total Population 75 and Older
1900	3.1 million	4.1	0.9 million	1.2
1940	9.0 million	6.8	2.7 million	2.0
1960	16.7 million	9.2	5.6 million	3.1
1980[a]	24.9 million	11.2	9.4 million	4.2
2000[b]	31.8 million	12.2[c]	14.4 million	5.5
2020[b]	45.1 million	15.5[c]	16.9 million	5.9[c]
2030[b]	55.0 million	18.3[c]	23.2 million	7.7[c]
2040[b]	55.0 million	17.8[c]	27.9 million	9.0[c]

[a]estimate.
[b]projection (base data of projection is July 1, 1976).
[c]projections based upon an intermediate fertility assumption (Series II) by the U.S. Census Bureau, and one immigration assumption (see text).
Source: US Bureau of the Census.

Medically, the elderly are not just "older adults" anymore than children are just "little people." The proper medical care of the elderly requires special approaches and an understanding of the physiologic, psychosociological and pathologic impacts of aging.(3) The elderly are not a homogeneous population. Tne significant differences in life expectancy at birth between whites and non-whites do not exist in life expectancy after age 65.(4)(Figure 3,4)

Fig. 3 **Life Expectancy at Birth, 1900 to 1978**

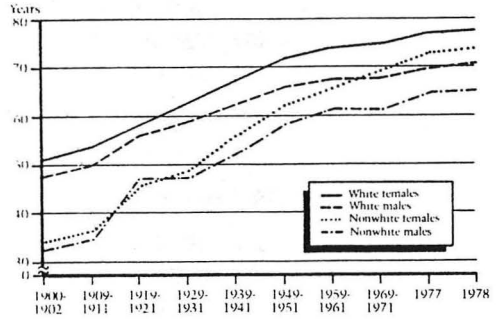
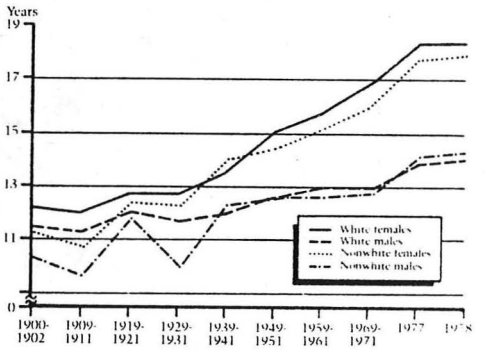
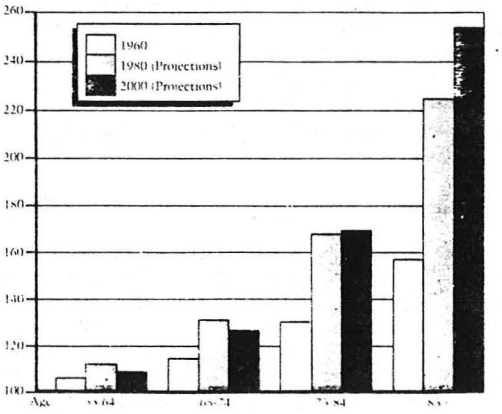


Fig. 4 **Life Expectancy at Age 65, 1900 to 1978**



A disproportionate number of women survive into advanced age, the "old-old" (over age 75) and the "extreme-old" (over age 85)(Figure 5), where the proportion of life expectancy characterized by dependency increases markedly(Figure 6). On the basis of money income alone, nearly one-sixth of the elderly live under the poverty level(Figure 7), however, over one-third of all unmarried older women, and two-thirds of black and hispanic older women, live at or below the federal poverty level(Figure 8).

Fig. 5 **Sex Ratios (Women per 100 Men) for Population Aged 55 and Over by Age Group**



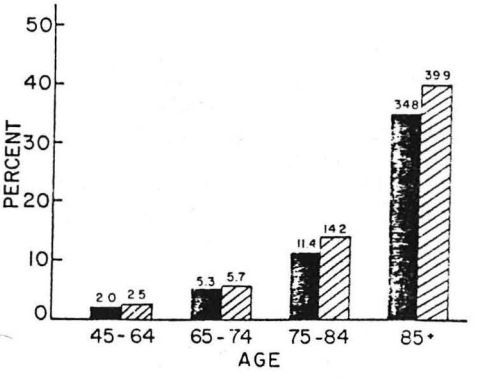


Fig. 6 Percentages of Adults, by Age Group, Requiring Assistance in Basic Activities (Walking, Bathing, Dressing, Using the Toilet, Transferring from Bed to Chair, Eating, Going Outside) and in Home-Management Activities (Shopping, Chores, Meals, Handling Money) because of Chronic Disease.

Solid bars denote basic activities, and hatched bars home-management activities.

Fig. 7 **Income Distribution of Persons Aged 25 to 64 and Over 65**

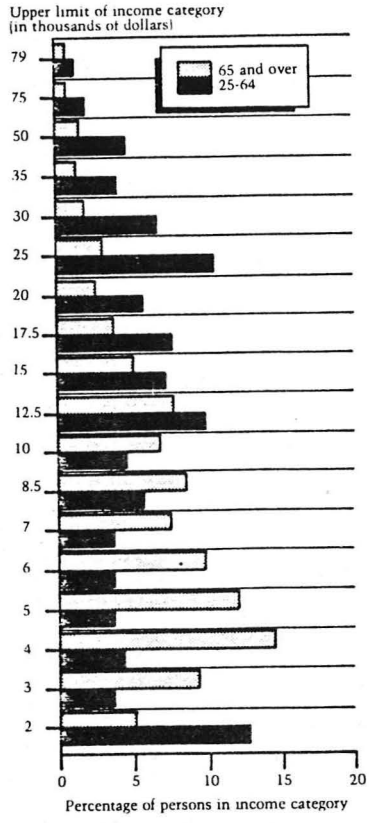
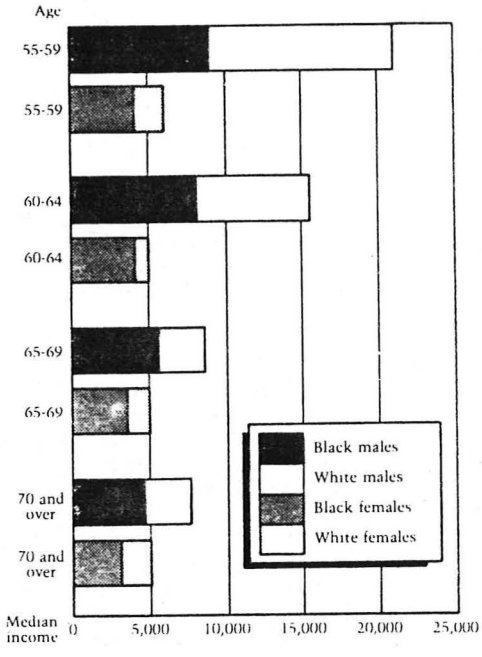


Fig. 8 **Median Annual Incomes of Persons Aged 55 and Over**



While the health of the aged is not as good as that of younger adults, most older people enjoy active, healthful lives. Seventy percent of elderly people report their health as good or excellent.(5) The number of pathologic conditions is strongly related to age and functional status, which is related directly to health care utilization. Community based elders have 3.5 important disabilities per person, compared to six in hospitalized elders.(6, 7). Only 5 to 6% of the elderly are institutionalized on a given day(4, 8), but of these 70% are women, generally widowed or unmarried.

Health Resource Utilization by the Elderly

Presently, the elderly consume one-third of all health care dollars, 36% of acute care hospital days, and more than 87% of the extended care facility days.(9) The over age 65 population consumes 25% of all prescriptions annually, and they represent the largest user group of over-the-counter remedies.(10) Physicians already dedicate 40% of their practice time to elders, which will increase to 75% by the year 2030 if practice patterns stay the same as they are today (and surely they will not!).

The utilization of physician services increases with advancing age from 4.4 visits per year in both under 17 and 17 to 44 age groups, to 5.1 for age 45-64, and to 6.4 in the over 65.(4) The enactment of Medicare did improve access to physicians for the elderly, but there is little evidence that the elderly "over use" physician services. In fact, there is a significant tendency for the elderly to explain away symptoms of serious illness and treatable diseases(6, 11) because they are also victims of "ageism" and feel they are "just getting old." Other factors contributing to underutilization include cognitive impairment, fear of the nature of underlying illness, structural barriers to access (costs, transportation, lack of social or family support), and the fear or unpleasantness of hospitalization or evaluation and treatment.(3) In contrast to younger patients who often present themselves for acute problems, the chronic nature of diseases in the elderly make it more likely that the physician will initiate the office visit.

The non-reporting of symptoms of underlying disease in the elderly could be less problematic if physicians took greater advantage of each visit by employing prevention-oriented and early intervention efforts.(12)

In a given year, about 10% of the United States population is hospitalized compared to 13% for the over age 65 population. The elderly also have longer hospital stays than other patients, 10.7 vs. 7.3 days in 1980, but this has changed since implementation of the prospective payment system (PPS) and Diagnostic Related Groups (DRGs).(13) Compared to the national average, Parkland had a lower length of stay (LOS) for the elderly even prior to the prospective payment system (base year 1982, 7.61 days vs. a national rate of over 11 days). The average LOS nationally has been reduced 11% by the new reimbursement system, but a different trend is emerging in some public hospitals.(14) With an increasing emphasis on day surgery and ambulatory care and with many empty beds in other hospitals now willing to compete for Medicare patients (even advertising waivers of co-deductibles), Parkland has seen a nearly 20% decline in Medicare admissions over the last two years. By 1984, Parkland's LOS for Medicare patients rose to 9.36 days (still below the national average). This marked increase reflects the rise in acuity level or severity of illness for admitted Medicare patients. Since DRG payments are a capitated rate and do not weigh the real cost associated with increasing levels of severity-of-illness as a reimbursement guide, Parkland may lose not only from decreased admissions, but also through underpayment of each case.

This phenomenon is not restricted to public hospitals, but it tends to occur most frequently in teaching hospitals with a tertiary care patient mix and a disproportionate share of charity care and bad debt. Recently, Horn and Associates(15), in Baltimore, evaluated the ability of the DRG classification system to account for severity of illness, and by implication, for the costs of medical care in six hospitals, three university teaching hospitals, two community teaching hospitals and one community hospital. Within each DRG, substantial differences were found in the distribution of severity of illness in different hospitals. Some hospitals treating larger proportions of severely ill patients had a wide range of severity within each DRG. Their findings indicate that unadjusted DRG's alone may unfairly and adversely discriminate against certain types of hospitals.

Readmission rates are also higher in the elderly. Recently Anderson and Steinberg(16) assessed the frequency with which 270,266 randomly selected Medicare beneficiaries were readmitted after hospital discharges between 1974 and 1977. Twenty-two percent of Medicare hospitalizations were followed by readmission within 60 days costing the Medicare program $2.5 billion per year (24% of all inpatient Medicare expenditures). In 1985 dollars this would exceed $8 billion per year. These authors also point out a small percentage (23%) of patients with multiple discharges (2 to 5 over three years) accounted for 80% of inpatient expenditures(Figure 9).

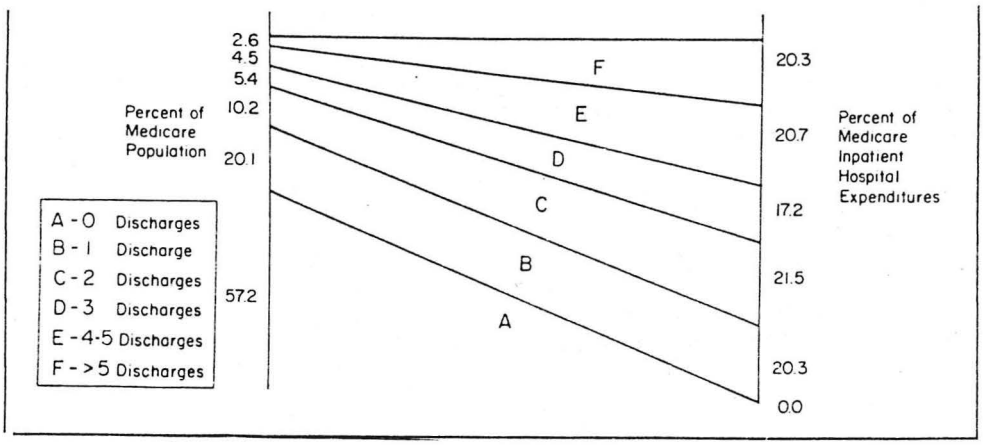


Fig. 9 Medicare Inpatient Hospital Expenditures Attributable to Beneficiaries with Various Numbers of Discharges. The graph shows the frequency with which various percentages of the Medicare population were discharged from an acute-care hospital between 1974 and 1977 and the percentage of Medicare s inpatient expenses attributable to each group. The percentage of Medicare beneficiaries in each group is identified on the left side of the figure, and the percentage of Medicare inpatient hospital expenditures attributable to each group is identified on the right. Both sides of the figure are drawn to scale, so that the width of a band on the left-hand margin reflects the percentage of Medicare beneficiaries in a group and the width of the same band on the right-hand margin reflects the percentage of inpatient expenditures attributable to the same group.

Rational or Rationed Approaches to Health Care for the Elderly

Case Management vs. Market Forces:

The recently enacted prospective payment system has created a series of perverse incentives affecting the elderly. Senator John Heinz (R-PA), Chairman of the Senate Special Committee on Aging recently said that elderly patients are being discharged "quicker and sicker" and "some may be discharged prematurely...too often into a no-care zone, without access to health care they urgently need."(17) If this phenomenon is accompanied by higher readmission rates, the potential savings from this effort will be lost along with the quality of care. Parkland's Geriatric Assessment Team (geriatric social workers, nurse practitioners and physicians) sponsored by a Robert Wood Johnson initiative tries to identify all high risks and frail elderly patients at Parkland to provide a proper link to out-of-hospital support in order to prevent the need for readmission.

The old cost-based reimbursement system afforded hospitals the opportunity to utilize allied health care staff to thoroughly evaluate individual patient's medical, psychosocial and economic needs. While research has recently demonstrated the preventive value of the geriatric assessment team and the special geriatric assessment unit, current prospective fixed payment systems will do little to foster the establishment of such efforts. Dr. Rubenstein and co-authors(18) recently showed that such a program which developed treatment and discharge plans, tailored to each patient's needs, could produce "significantly longer survival and less use of acute care and long-term institutional services after one year of follow-up" compared to routine care in elderly counterparts that did not receive such an intervention.(Table 2, Figure 10.) Savings created by the avoidance of acute hospitalization and nursing home care placements during that first year of follow-up "more than recouped" the cost of the additional days of intermediate hospital stay on the geriatric assessment unit (Table 3), but also improved the patient's basic functional status.(Figure 11) These authors estimate that such units could cut nursing home admissions by 200,000 yearly. This study was done at the Sepulveda Veterans Administration Medical Center, in a portion of the "public sector" that must face the challenge of dealing with a large increase in elderly patients for which they are also responsible financially. The support of such studies in the public sector and the initiatives of the Robert Wood Johnson Foundation become even more important since innovation is not likely to arise in a system where prospective payment takes away any incentive on the part of hospitals to bear the costs of such services. The logic of improving survival and function as well as reducing overall costs to society should be compelling reasons to reassess the incentives created by prospective payment.

Table 2. Location at Discharge and 12 Months after Random Assignment to the Geriatric Evaluation Unit (GEU) or to a Control Group.

Location	At Discharge			At 12 Months		
	GEU (N = 63)	Control (N = 60)	P*	GEU (N = 63)	Control (N = 60)	P*
	% of patients (no.)			% of patients (no.)		
Home/board and care	73.0 (46)	53.3 (32)	<0.05	55.6 (35)	36.7 (22)	<0.05
Nursing home	12.7 (8)	30.0 (18)	<0.05	17.5 (11)	11.7 (7)	NS
Hospital	0	1.7 (1) †	NS	3.2 (2)	3.3 (2)	NS
Died	14.3 (9)	15.0 (9)	NS	23.8 (15)	48.3 (29)	<0.005

*The GEU and control groups were compared for each category by a z-test of proportions. NS denotes not significant.
†One patient was still hospitalized 12 months after random assignment.

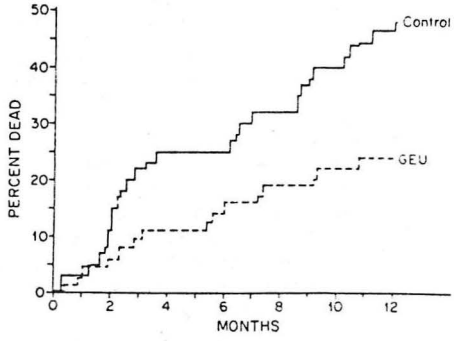


Fig. 10 One-Year Mortality Curves for Geriatric Evaluation Unit (GEU) and Control Patients.

Table 3. Institutional Days and Associated Direct Veterans Administration (VA) Costs 12 Months after Random Assignment to the Geriatric Evaluation Unit (GEU) or the Control Group.

Institutional Category (Current VA Costs)	GEU	Control	GEU	Control	GEU	Control	GEU	Control
	mean days/patient		*VA costs/patient*		*mean days/yr survived*		*VA costs/yr survived*	
VA hospital days								
Intensive care ($770/day) *	3.0	2.2	$2,310	$1,694	3.5	3.0	$2,695	$2,310
Acute care ($308/day) †	18.1	34.2	$5,575	$10,534	21.1	46.8	$6,499	$14,414
Intermediate care ($117/day)	79.5	28.3	$9,302	$3,311	92.5	38.8	$10,823	$4,540
Non-VA hospital days	1.9	2.8	—	—	2.2	3.8	—	—
Nursing-home days ($86/day) ‡	25.8	55.7	$2,219	$4,790	30.0	76.3	$2,580	$6,562
Total institutional days	*128.3*	*123.2*	*$19,406*	*$20,329*	*149.3*	*168.7*	*$22,597*	*$27,826*

*This figure represents the arithmetic mean of daily costs for the medical, surgical, and coronary intensive-care units.

†This figure represents the mean daily cost for surgical and medical acute-care beds.

‡This figure represents the mean daily nursing-home cost for both the Veterans Administration and community nursing homes.

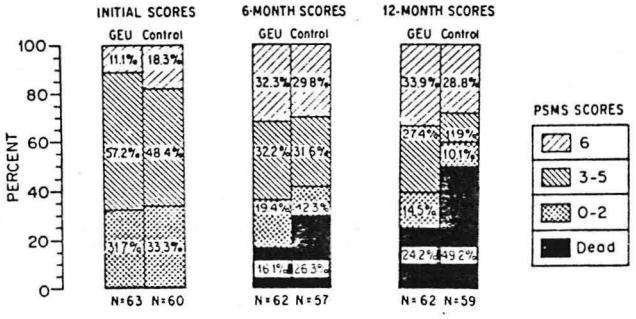


Fig. 11 Comparison of Basic Functional Status of Geriatric Evaluation Unit (GEU) and Control Patients at the Time of Random Assignment and 6 and 12 Months Later. The Personal Self-Maintenance Scale (PSMS)[8] was used to determine functional status. A score of 6 indicates complete independence in the six activities of daily living: ambulation, bathing, grooming, dressing, using the toilet, and feeding. Lower scores indicate fewer functional abilities.

As a public teaching hospital, Parkland has found it more and more advantageous to act as a catalyst in the community development of services for the elderly, particularly the frail and minority elderly. We have taken a more aggressive advocacy stance in such programs as Elder Abuse. We have tried in recent years to work as the hub (tertiary and secondary care) of a continuim of care made up of a consortium of other public and non-profit providers based in the community (Access Centers for the Elderly (ACE), Visiting Nurse Association, Meals-On-Wheels, nutrition centers, Area Agency on Aging, etc.) We will continue to emphasize primary and secondary prevention, case management to achieve maximal function and independence and we will foster multidisciplinary training programs to address the needs of the elderly. The attitude that health care is a business, selling commodities like any other business, will prevail in certain sectors of the hospital industry. Some hospitals will disinvest in services to the elderly in order to be more competitive. Hospitals that continue to view health care as a community service and a public trust will have to find business-like, cost-effective approaches to maintain a delivery of high quality, accessible and affordable health care for the elderly. It would certainly help to have reimbursement incentives based upon rational, not rationed, budget deficit driven scenarios.

As Woody Allen aptly stated "Death is a great way to cut down on expenses". A recent descriptive study offers an indication of the problems that develop in adults when access to affordable care is decreased. A comparison was made between hypertensive patients cut from the California Medi-Cal program and a group of comparatively sicker hypertensive controls who continued to receive coverage.(19) The diastolic blood pressure in the study group rose an average of 10mmHg compared to an average reduction of 5mmHg in the control group. Data from the Framingham Study indicate that an average 10mmHg increase in diastolic blood pressure increases a persons risks of dying prematurely by 40 per cent.(20) In this study, five deaths did occur in the study group cut from Medi-Cal, three of which were felt to be preventable by better blood pressure control. No hypertensive deaths occurred in the control group. An increase in morbid events in contrast to mortal events increases total costs and will offset any "savings" from a reduction in the provision of subsidized health care. The lack of a rational health care policy for this nation is typified by the public's interest (despite cost implications) in recipients of artifical hearts (the "identified life") and seeming disregard for the provision of cost effective preventive health interventions for the very young, the elderly and the poor. This is almost as schizophrenic as the simultaneous federal subsidy of the tobacco industry and the desire to freeze Medicaid expenditures to control "spiraling" health care costs. The elderly are among the most vulnerable in such a policy vacuum.

Drug Therapy--Friend and Foe in the Elderly:

Another source of hospital admissions, readmissions and excess medical costs for the elderly that perhaps could be reduced results from adverse drug reactions (ADRs). Admission rates from drug induced illness in over age 60 patients were 15 times higher than in younger patients in a hospital-based study that also revealed an admission rate of 3% from ADRs(21). In 1976, it was estimated that such admissions cost $3 billion per year ($9 billion in 1985 dollars)(22). While in the hospital, ADRs occur in 10 to 18% of patients(23), with the elderly again being at highest risk. In one survey of 700 hospitalized patients, drug induced illness was found in 25% of patients older than 80 years compared to 12% in patients during their fifth decade of life(24). Similarly another large hospital survey revealed a prevalance of ADRs of 12 to 17% in 70 to 90 year olds compared to 3% in those aged 10 to 30 years(25).

Despite the fact that elders are well represented as a high risk group for ADRs, they are usually underrepresented in new drug trials. Drugs that have an acceptable margin of safety in young subjects may be much more dangerous in elderly patients. Pre-market testing of drugs intended for geriatric patients should follow systemic guidelines concerning the age of subjects.

Hospital based clinical pharmacy services need to be directed at the identification and prevention of ADRs. Just as a small reduction in readmission rates justify the salaries of geriatric social workers and nurse practitioners on a geriatric assessment team, the prevention of ADR's can decrease hospital length of stay, improve quality of care, and at the same time lower costs. Again, under prospective payment many hospitals have cut, not expanded such ancillary support staff. Regulatory and reimbursement barriers have replaced preventive interventions as the cost containment method of preference.

In 1984, an estimated $4,202 per capita was spent for personal health services for the over age 65, a 3.4 to 1 ratio over the under age 65 population(4). Institutions, hospitals and nursing homes received 45% and 21% respectively whereas physicians received 21%, while all others received 13%. Despite the fact that just under two-thirds of the health care costs of older people are paid for by public programs, primarily Medicare (49%) and Medicaid (13%), the elderly pay one-third of their health care costs out-of-pocket, a strain that is greater than for other age groups. Surprisingly, out-of-pocket expenses for health care are a bigger proportion of total living costs for the elderly than before Medicare was enacted.(26) Because they are not covered by Medicare or most other third party insurance schemes, drugs are the second highest out-of-pocket health care expense for this group.

The elderly are high health care consumers and the fact that 50% or more of the income for over half of the married and two-thirds of the non-married beneficiaries derive from Social Security benefits, mean that a new structural poverty class is emerging that will increasingly compete for scarce resources with other recipients of charity care. Clearly, economic, psychological, and social support problems will become more serious as the societal aged dependency ratio increases(Figure 12). Proposals to limit Social Security cost-of-living allowances could increase the number of elderly below the federal poverty line by as much as 72 per cent(27) which would further aggravate an already crisis situation.

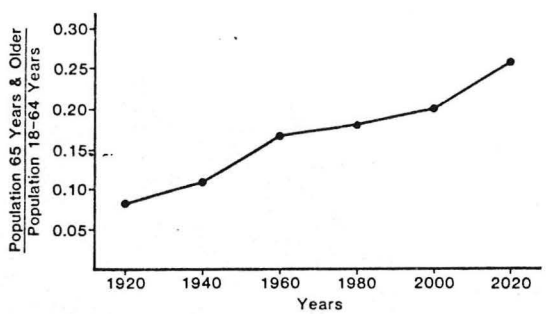


Figure 12 Societal aged dependency ratio: 1900-2020. (Source: U.S. Bureau of the Census.)

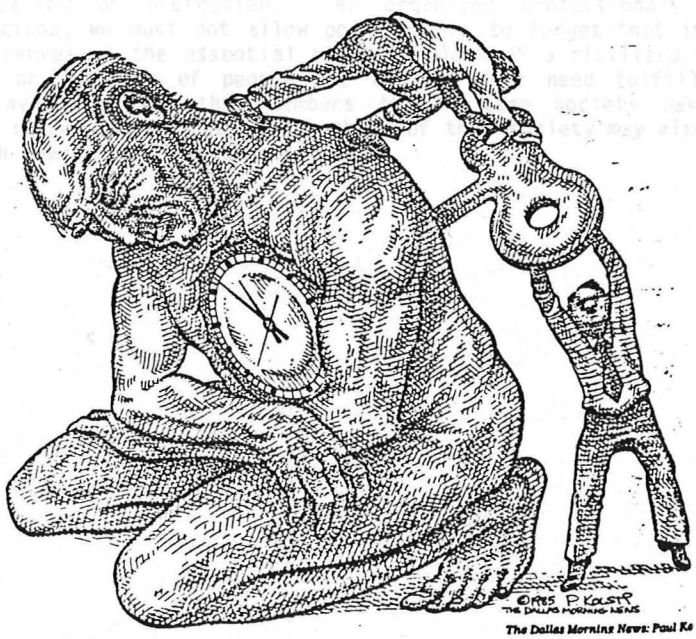
The Challenge to Medical Education

In 1982, William Butler, M.D. the first director of the National Institute of Aging, reported that less than half of our nation's medical schools offered an elective in geriatrics.(28) Worse yet, only 2.5% of medical students actually took advantage of these electives. Election hardly seems the fair approach to our current students, the generation of physicians, that will have to face head-on the medical challenges of an aging society.

Currently, medical students present the octagenarian in much the same fashion as a 25 year old, paying remarkable attention in history gathering to genetic illnesses in remote relatives or to queries about high cholesterol, failing to evaluate the extent of social and economic supports available to the patient upon discharge.

Within our training programs, the wide spectrum of interaction between normal aging processes and diseases are often not appreciated. The disease-oriented model with its definite bias toward definitive diagnoses and cure is more comfortable than a model that emphasizes "maintenance of functional capacity"(29). The house staff officer who fails to do a "complete work up"(30) on an elderly patient may be judged as lazy, callous, uncaring or incompetent by peers and faculty alike. The proper faculty role model is critical to the housestaff officer's development of clinical judgment in balancing the risks against the benefits (utility) of diagnostic interventions in regard to functional status. Stated another way, each investigative decision should be based on the "principle of minimal interference."(31)

It may be argued that health promotion and disease prevention strategies, while important because they extend functional life, have not resulted in cost reduction because of "heroic" and expensive interventions made at the very end of the life span. This is a period currently characterized by hospital admission, aggressive diagnostic interventions and high utilization of life support and intensive care technologies. Often these interventions are undertaken on behalf of a patient (or family) without an understanding of the patient's desires. Health care dollars consumed "doing everything possible" may be wasted, but more importantly they may also be doing harm by extending the "pre-death" period of severe disability, dependence, and suffering(32, 33).



The Dallas Morning News: Paul Ko

A healthier, longer life, capped by a compression period of morbidity, is a worthwhile goal, if therapeutic priorities can be reordered during the pre-death period from cure to care. If as some argue, morbidity will not decline parallel to the reductions of mortality in the "old-old" and "extreme-old" populations(34, 35), health care needs and costs may dramatically increase. In either case, physicians in training should be exposed to the conflicts of scarce resource allocation through formal bioethics discussion groups and seminars, as well as informally, on ward rounds. Housestaff should be at least introduced to the concept and role of hospital bioethics committees.

A thorough body of knowledge concerning age-related physiologic changes should be incorporated into medical school curricula. Communication skills also need to be developed that are sensitive to the unique values, goals and fears of the elderly.

Teaching the "principle of minimal interference" (balancing each step) requires a great effort and commitment on the part of an attending so that the young housestaff officer will not interpret it as a veiled argument for rationing. If the attending physician role models as an advocate for each individual elderly patient, housestaff will be less likely to fall prey to the "human-capital" arguments against the allocation of scarce resources to the elderly. These economic arguments are a new form of bigotry that ignores respect for human life, the realities of pain and suffering and the contributions that elders make to the quality of life in our society. As Fein pointed out so well(36), "We live in a society, not in an economy."

The physician educator, should reassert to his/her students the importance of the individual's needs over the supposed needs of society, in other words, reassert the meaning of profession. As organized professionals and as individual physicians, we must not allow policymakers to forget that it is the individual that serves as the essential building block of a civilized society. When any person or subgroup of people are denied basic need fulfillment or freedom rights available to other members of the same society based upon religion, creed, color, sex or age, all members of that society may also become less important in the name of the common good.

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Hypertension in the Elderly

Ron J. Anderson, M.D.
President & Chief Executive Officer
Parkland Memorial Hospital
Associate Professor, Internal Medicine
The University of Texas Health Science
Center at Dallas

Part II
Parkland Medical Grand Rounds
7/18/85

Part II: Hypertension in the Elderly

HYPERTENSION IN THE ELDERLY

Tne cost of medical care for the elderly is staggering. In 1984, the estimated per capita costs for medical care in persons 65 years of age and older was $4,202.(1) In 1980, the U.S. Census revealed 24.9 million persons age 65 or over (11.2% of total population) which is projected to increase to 31.8 million (12.2%) by the year 2000, and 55 million (18.3%) by the year 2030.(2) These projections coupled to the high utilization of health care resources by the elderly have enormous implications for this country's health care system.

Over one-half of all mortality in the age over 65 population is due to cardiac and cerebrovascular disease. The disability and loss of functional status related to these disorders affect the quality of life of millions of elderly people. In the past, such degenerative diseases were too often considered inevitable consequences of a normal aging process that proceeded at different rates in different individuals. Aging does predispose to these cardiovascular disorders, but hypercholesterolemia, smoking and hypertension accelerate arteriosclerosis. Hypertension is perhaps the most common and potent contributor to stroke, heart failure, and coronary disease in all age groups.(3) In the over 65 population, hypertension is the leading risk factor for myocardial infarction and thrombotic stroke. The increased detection and treatment of hypertension in the general population has been associated with a recent decline in the national prevalence of morbid events related to cardiovascular disease.(4, 5)(Figure 1)

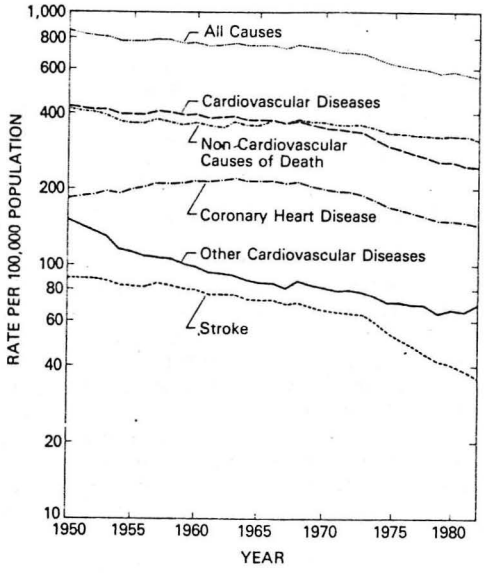


FIGURE 1. Death rates in the United States, 1950–1982, for all causes of death, all cardiovascular causes and subgroups, and all noncardiovascular causes.

Goldman and Cook(6) attribute over one-half of this reduction in ischemic heart disease mortality to reductions in serum cholesterol levels and cigarette smoking. Coronary care units, medical treatment of ischemic heart disease and hypertension were listed as the leading contributors to the remainder of the decline. Despite multiple studies on the risks, epidemiology and treatment of young and middle-aged patients with hypertension, the group with the highest prevalence of this disorder, the elderly, have been the least well studied. Until recently, drug trials were prone to avoid the inclusion of elderly hypertensive subjects. For example, the age distribution of 1,000 hypertensive patients in 41 randomly selected studies from 1973 to 1977 were reviewed by Koch-Weser.(7) He found that only 10% of the subjects were 61 years or older. Tne small number of elderly patients and the short-term nature of safety and efficacy studies made it statistically impossible to identify the risks of hypertension and tne benefit of blood pressure reduction from this pooled information. Additionally, the paucity of elder involvement in these therapeutic trials ignored the unique problems of drug handling and toxicity in the aged.

More recently, large clinical trials have focused on the elderly hypertensive to learn more about the prevalence, risks, pathophysiology and benefits of therapy. At the beginning of these studies, some simple questions were asked: Is elevated blood pressure in the elderly a disease with risks or a marker of the aging process? If elevated blood pressure does represent a risk, can that risk be reduced by treatment? Is hypertension in the elderly a different disease than in the young, particularly as it relates to isolated systolic hypertension? What are the special needs of the elderly hypertensive? Will therapy, even if successful in prolonging life, improve the functional status of patients? A number of these questions have been answered and important clinical trials to answer the others are underway. The insight from these queries, if properly translated and applied, offers opportunities for the prevention of disability, the preservation of function and a further extension of quality life in our elderly population.

Definition and Prevalence of Hypertension in the Elderly; A Disease or a Marker of Aging?

Tne aging process proceeds at different rates in different individuals, making the definition of "elderly" somewhat arbitrary. In this review, the elderly are defined as 65 years of age and older. Likewise, the definition of hypertension is arbitrary. Cardiovascular risks are directly related to systolic and diastolic blood pressure over the entire range of normal and elevated blood pressure with no level defining an abrupt change in risk. For this review, because most epidemiologic studies use it, the World Health Organization's definition of hypertension is used: a supine systolic blood pressure of 160 mmHg or greater or a diastolic blood pressure of 95 mmHg or greater, or both, regardless of age.

Diastolic blood pressure tends to rise with age until about age 60 and thereafter falls in both men and women, whereas systolic blood pressure continues to rise with age.(8, 9) Fifteen percent of white men and women and 30 to 40 percent of black men and women over the age of 65 have diastolic blood pressure greater than or equal to ($\leq$) 95 mmHg.(9) Isolated systolic hypertension, as defined by a systolic blood pressure $\geq$ 160 mmHg with a diastolic blood pressure $\leq$ 95 mmHg, is also common. The incidence of isolated systolic hypertension increases steeply after age 55 in both sexes, but is even greater in females(10), reaching a prevalence of 25 to 30 percent in the age 80 or over population.(11)(Figure 2)

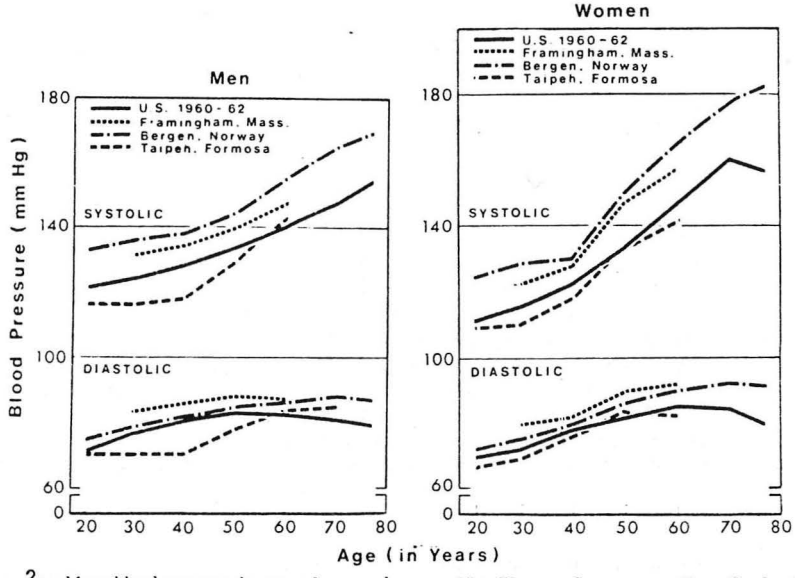


Figure 2. Mean blood pressure, by age, of men and women 18 to 79 years; four surveys. (From Gordon T: Blood Pressure of Adults by Age and Sex, United States 1960–62. National Center for Health Statistics, PHS Publ. 1000, ser. 11, no. 4, 1964.)

The elderly also tend to have disproportionate systolic hypertension, that is a systolic pressure greater than 2X (diastolic blood pressure - 15). Colandrea and colleagues(12) found the incidence of isolated systolic hypertension in 3,245 elderly subjects (average age approximately 69 years) to be 13.9% during an initial examination, but the incidence fell to 2.7% if two subsequent blood pressure determinations were utilized. In contrast, Wing, et al(13) found an increased prevalence of isolated systolic hypertension after the second and third of three blood pressure readings (during one clinic visit). This pattern is the reverse of what is usually found in essential hypertension in a younger population. Diastolic variability was actually greater than systolic variability, and unlike essential hypertension, prevalence of isolated systolic hypertension varied more by sex than by race, being 60 to 100% more likely in females. (Fig. 3a&b) Both of these studies point out the lability of isolated systolic hypertension in the elderly, nevertheless, most population studies attempting to assess hypertensive risk utilized a single casual blood pressure recording which had a high correlation for risk at any age.(14)

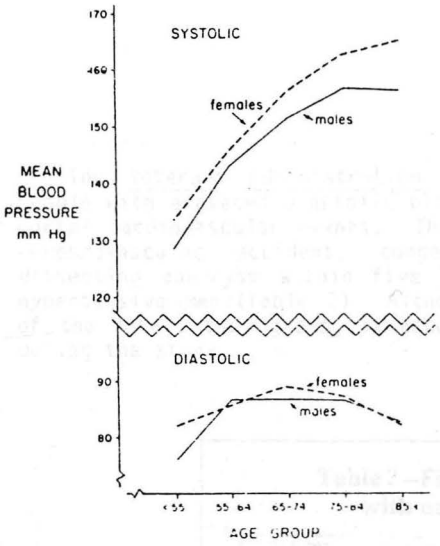


Figure 3a.

Mean initial blood pressure in Leisure World study population.

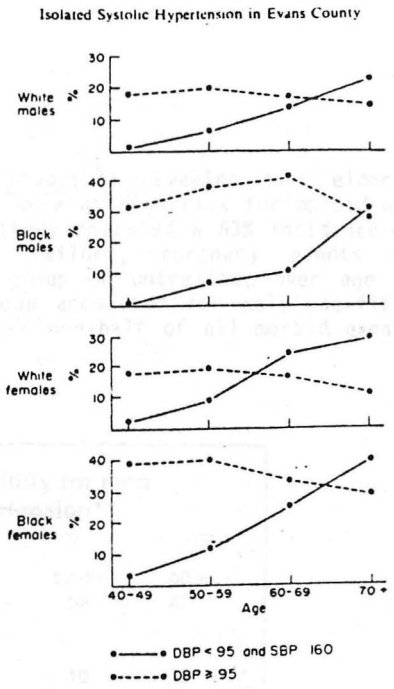


Fig. 3b

Risk of Hypertension in the Elderly

The common occurance of a rise in blood pressure with aging may have led to the misconception that high blood pressure was a part of the normal aging process and that it may not be detrimental to some older persons.(15) The contribution of hypertension to cardiovascular disease does not diminish with increasing age in any major controlled study. Instead, the evidence accumulated thus far implicates hypertension as a major cause of morbidity and mortablity in old, as well as young patients.

The Framingham Study, started in 1949, has provided considerable insight into the risks and benefits of treatment for elderly hypertensives. Data from this study have revealed at least a two-fold increase in mortality from all causes in hypertensive persons compared to normotensive persons (≤ 140 mmHg), over all age groups.(16) Specifically, the average annual incidence of cardiovascular events increased two-fold in mildly hypertensive men and women between the ages of 65 to 74 with the bulk of the excess mortality due to cardiovascular disease.(Table 1)

Table 1. Average annual incidence of cardiovascular events per 1,000 population according to diastolic blood pressure (mm Hg)

Age-group	Men			Women		
	<90	90-109	≥110	<90	90-109	≥110
45-54 yr	9.5	17.7	33.6	3.0	5.9	13.6
55-64 yr	18.0	37.7	62.2	10.2	15.6	39.4
65-74 yr	24.2	42.9	55.6	17.2	32.4	54.5

Based on 18-year follow-up of Framingham study, by Kannel and Gordan.

Tne Veterans Administration Cooperative Study(17) revealed that elderly people with elevated diastolic blood pressures were at high risk for morbid and mortal cardiovascular events. This landmark study revealed a 63% incidence of cerebrovascular accident, congestive heart failure, coronary events or dissecting aneurysm within five years for a group of untreated, over age 60 hypertensive men.(Table 2) Although this group accounted for only one-fifth of tne total study group, it accounted for over one-half of all morbid events during the study.

Table 2 –Five-year morbidity for men with untreated hypertension*

Age	<50	50–59	60+
Total number	99	52	43
Percentage with			
Cerebrovascular accidents	5	10	23
Congestive heart failure	1	2	20
Accelerated hypertension	5	4	0
Coronary artery disease	4	8	12
Dissecting aneurysm	0	2	2
Overall morbidity (%)	15	27	63

*Diastolic blood pressures of 90 to 114 mm Hg.
From the Veterans Administration Cooperative Study: *Circulation* 45:991, 1972, by permission of the American Heart Association, Inc.

The Chicago Peoples Gas Company Study(18) of 1,233 white men, age 40 to 59 years old, revealed that isolated systolic hypertension (group 3)(Table 3) had a two-fold mortality rate compared to normotensive men (group 1) and a mortality rate almost as high as in men with diastolic hypertension (group 2). They also found that the risk of both coronary death and stroke was roughly 2½-fold greater for men 65 to 74 years of age compared to those 60 to 64 years old.

Table 3–Baseline blood pressure and 15-year mortality of 1233 white men 40 to 59 years old and free of definite coronary heart disease
(1958 Chicago Peoples Gas Company study)

Group	Blood pressure status	Number of men	Death from all causes		Death from cardiovascular and renal causes		Death from coronary heart disease only	
			Events	Rate*	Events	Rate*	Events	Rate*
1	Systolic <140 Diastolic <90	782	119	163	61	83	44	58
2	Diastolic ≥90	257	90	323	49	174	33	117
3	Systolic ≥140 Diastolic <90	194	58	277	30	156	21	118
	Rate Ratio: 3 vs 1			1.70		1.88		2.03

*Per 1000 population, adjusted on the basis of age by 5-year age groups to the whole cohort.

From Dyer AR, Stamler J, Shekelle RB, et al: Hypertension in the elderly. *Med Clin North Am* 61:513, 1977.

A ten year longitudinal survey of 191 institutionalized female elderly subjects in France (mean age 80-range 61 to 100 years), designed to capture the incidence of all cardiovascular events, found that isolated systolic hypertension, as well as diastolic hypertension, was significantly correlated with the incidence of strokes and myocardial infarction (2-fold increase). This increased risk was independent of blood cholesterol and blood sugar levels which did not appear to be major risk factors in this population.(19)

Previously, the Chicago Stroke Study(20) found that systolic blood pressure was an important as diastolic blood pressure in predicting the incidence of stroke. This study found a 2½-fold incidence of stroke in subjects with isolated systolic hypertension compared to normotensive subjects. These findings are consistent with the results of the Framingham Study where both diastolic and isolated systolic hypertension were more predictive in the elderly than in the young.(Figure 4) This association with cerebrovascular morbidity was independent of the degree of arterial rigidity, a physiologic change accompanying aging.(21)

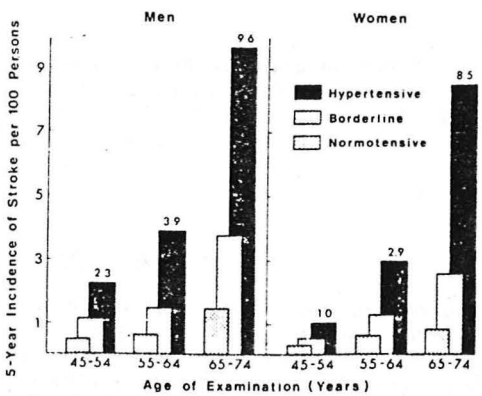


Figure 4 Incidence of stroke according to hypertensive status. Men and women ages 45 to 74 years in Framingham study. Hypertensive: DBP > 95 mm Hg; Borderline: DBP 90–95 mm Hg; Normotensive: DBP < 90 Hg. Note that the relative risk for hypertensive persons does not decline with age. (From Kannel WB, Wolf P, Daw T. Hypertension and cardiac impairments increase stroke risk. Geriatrics, 33:71–83, 1978. With permission *Geriatrics.*)

Tne Pooling Project Research Group(22) by combining several comparable studies found a striking correlation between the first coronary event and elevated diastolic or systolic blood pressure regardless of age. In this study, hypertension was the most discriminating predictor, aside from advancing age, of the development of angina pectoris, myocardial infarction, or sudden death. For example, men aged 55 to 64 with systolic blood pressures between 170 to 179 mmHg, had an annual incidence of coronary events, over 40 per 1,000 compared to less than 20 per 1,000 in men with a systolic blood pressure between 120 and 140 mmHg.(23) In the older members of this cohert, aged 60 to 64, who were initially free of clinical coronary artery disease, a diastolic blood pressure of 95 mmHg or above was associated with a 3.7 times increased risk for a major coronary event compared to men with a diastolic blood pressure below 80 mmHg.(22) In subjects studied after the onset of clinical coronary disease, the disease ran a more rapidly fatal course in those who were hypertensive.(24)

Tne evidence for the role of hypertension in the development of congestive heart failure is convincing. The Framingham Study indicates that hypertension precedes the development of congestive heart failure in 75 percent of cases(25) and the relative risk of developing congestive heart failure is six times greater in hypertensives than in normotensives.(26) This increased risk is even slightly more prominent in the subpopulation of elderly hypertensives (age 65 to 75). Even prior to clinically apparent congestive heart failure, left ventricular hypertrophy (by electrocardiogram) and left ventricular enlargement (by chest roentgenogram), correlate closely with the degree of hypertension at any age, including ages 65 to 74.(26) Left ventricular hypertrophy was associated with a 10-fold increased risk for congestive heart failure. In the Veterans Administration Cooperative Study,(17) nine elderly men(20%) with diastolic blood pressure of 90-114 mmHg, randomized to placebo therapy, developed congestive heart failure, whereas none did in the treatment group.

Even excluding patients with prior or co-existing coronary artery disease, and despite routine management with diuretics and cardiac glycosides, 20% of men and 14% of women with congestive heart failure died within one year in the Framingham Study.(26) By five years, a projected mortality rate of 58% and 42%, in men and women respectively, was anticipated.

Hypertension is one of the most common diseases of the elderly. It is not just a marker of aging. Now that the associated risks are well documented, even for isolated systolic hypertension, the next key question is whether or not treatment diminishes the risk.

Tne Effects of Treatment on Risk Reduction

Tne fact that diastolic and systolic hypertension are associated with an increased risk for cardiovascular disease in the elderly obviously does not prove that treatment will favorably alter these risks. A body of evidence is emerging that careful blood pressure reduction in elderly hypertensives is possible, and that it can extend functional life.

In a retrospective, non-randomized study of 183 institutionalized patients 60 to 69 years of age, Priddle and co-workers(27) found the mortality of 100 patients treated with a thiazide diuretic to be one-half that of 83 comparable patients in the untreated group, largely because of a reduction in the incidence of stroke and cardiovascular disease. Although the results suggested a benefit of treatment, the nature and bias of the study allowed no definite conclusions.

In the Veterans Administration Cooperative Study(17) only 81 patients over the age of 60 with mild to moderate (between 90 to 114 mmHg) hypertension were included.(Table 4) Patients older than 75 years were automatically excluded. All patients were randomized to either no treatment or treatment with a combination of hydrochlorothiazide, reserpine, and hydralazine. Treatment was effective in preventing morbid events, primarily stroke and congestive heart failure by 50% in all age groups. In the over 60 year age group, the morbidity was 62.8% and 28.9% for the control and treatment groups, respectively. Treatment prevented 33.9 morbid events per 100 subjects in the over 60-age group compared to 8.3 events per 100 subjects in the under 50-age group, suggesting an increased benefit for the elderly hypertensive. When analyzed separately, the treatment group with diastolic glood pressures greater than 105 mmHg had the best risk reduction. Still, the small size of this subpopulation led the investigators to conclude that their data was too scanty for confident analysis.(28)

Table 4 Incidence of cardiovascular events with respect to age at randomization in hypertensive patients receiving treatment and in hypertensive controls

Age-group	Treated group		Control group	
	No. patients	No. events (%)	No. patients	No. events (%)
< 50 yr	102	7 (6.9)	99	15 (15.2)
50-59 yr	46	4 (8.7)	52	14 (26.9)
≥60 yr	38	11 (28.9)	43	27 (62.8)
Total	186	22 (11.8)	194	56 (28.9)

Adapted from Veterans Administration Cooperative Study Group on Antihypertensive Agents.

The Hypertension Detection and Followup Program (HDFP) Cooperative Group(29) compared stepped-care in special blood pressure clinics to the quality of blood pressure control routinely available by community referral. The stepped-care approach did achieve a further reduction in diastolic blood pressure averaging only about 5 mmHg. A beneficial effect of tighter blood pressure control was seen across all age groups, but a 17.2 percent reduction in mortality was achieved in the stepped-care patients, aged 60 to 69, primarily due to a reduction in cardiovascular deaths (16.4%). This study, for ethical reasons, did not use a placebo-treated control population so that comparisons are only possible between two different treatment styles. In this light, the HDFP has been criticized since the stepped-care patients had fewer non-cardiovascular deaths as well and may have benefited from the design of the trial.(30) Still, the large conert of 60-69 year old subjects, 2,376 prior to randomization, makes this one of the largest and most important studies to date.

In later analyses of the HDFP, a 44.3% reduction in the incidence of stroke in stepped-care patients, aged 60 to 69, was documented.(31) The greatest reduction in strokes for stepped care versus referral care patients occurred in the older age groups: 44.3% for ages 60-59, 33% for ages 50-59, and 24.6% for ages 30-49.(32) Conversely, the 30-49 year aged stepped-care patients showed a greater reduction of myocardial infarction than their referral counterparts, with only marginal benefit in the older stepped-care patients. While the autnors attribute these benefits solely to a further reduction in blood pressure, the more comprehensive medical care clinic model may have also been at work. The HDFP performed another valuable service by demonstrating that hypertension can be controlled without serious side effects in the majority of elderly patients. Over 5 years, 79.4 percent of the older stepped-care subjects remained under active care and 81 percent of those achieved their goal diastolic blood pressure.(33)(Table 5)

Table 5.

Incidence of selected adverse drug reactions by age among Stepped Care participants in the Hypertension Detection and Follow-up Program, 1972-1979*

Adverse reaction	Age (years)							
	30-39		40-49		50-59		60-69	
	No.	Rate/100*	No.	Rate/100*	No.	Rate/100*	No.	Rate/100*
Arrhythmias	3	0.5	12	1.0	15	1.2	3	0.4
Hypotension	10	1.5	8	0.7	8	0.6	8	1.0
Orthostatic hypotension	5	0.8	15	1.3	12	1.0	4	0.5
Minor gastrointestinal	37	5.7	78	6.7	93	7.5	41	5.2
Peptic ulcer/gastrointestinal bleeding	0	0	6	0.5	9	0.7	5	0.6
Liver enzyme abnormalities	7	1.1	6	0.5	8	0.6	4	0.5
Arthritis/arthralgias	8	1.2	10	0.9	8	0.6	4	0.5
Rash	17	2.6	37	3.2	46	3.7	26	3.3
Nasal stuffiness	22	3.4	40	3.4	30	2.4	10	1.3
Impotence	33	5.1	45	3.9	63	5.1	12	1.5
Depression	28	4.3	58	5.0	40	3.2	11	1.4
Nightmares	19	2.9	36	3.1	28	2.3	8	1.0
Dizziness	28	4.3	51	4.4	57	4.6	29	3.7
Lethargy/drowsiness	46	7.1	96	8.2	74	6.0	24	3.1
Weakness	19	2.9	41	3.5	47	3.8	25	3.2
Hypokalemia	13	2.0	21	1.8	17	1.4	8	1.0
Gout/hyperuricemia	5	0.8	16	1.4	22	1.7	6	0.8
Diabetes/hyperglycemia	5	0.8	18	1.6	27	2.1	13	1.7
Gynecomastia	10	1.5	16	1.4	31	2.5	8	1.0

* Expressed as incidence of individuals who had a drug discontinued during the five-year clinical trial secondary to an adverse drug reaction per 100 active Stepped Care Hypertension Detection and Follow-up Program participants who were not taking antihypertensive medication at baseline.

The National Heart Foundation of Australia Study(34) looked at 582 patients, 60 to 69 years of age with mild hypertension (diastolic between 95 and 109 mmHg). Subjects were carefully screened to exclude patients with concommitant diseases prior to entry. Subjects were then randomized to placebo or active treatment (a thiazide diuretic followed by methyldopa, a beta blocker, or clonidine). In the treated group, 27 morbid events (31.0/1,000 patient-years) occurred compared to the placebo group that experienced 42 morbid events (50.8/1,000 patient-years), a 30 percent reduction. The design of this study is clean, but its strength becomes a weakness since few elderly hypertensive patients will be affected by this one disease process alone.(35)

The European Working Party on High Blood Pressure in the Elderly Trial (EWPHPE)(36), a double-blind randomized placebo-controlled trial of antinypertensive therapy in patients over age 60 was started 12 years ago. Entry criteria included both a sitting diastolic blood pressure on placebo treatment in the range of 90-119 mmHg and a systolic pressure in the range of 160-239 mmHg. Patients were exlcuded from the trial if they had curable causes of high blood pressure, certain complications such as grade III or IV retinopathy, congestive heart failure, history of cerebral or subarachnoid hemorrhage, concurrent diseases such as hepatitis or cirrhosis, gout, malignancy, and diabetes mellitus requiring insulin treatment. Eight hundred and forty patients were randomized to either active treatment (N=416) (one nydrochlorothiazide + triamterene capsule) or to matching placebo (N=424). The placebo and active treatment groups were similar in age, sex, blood pressure, weight, height, and cardiovascular complications on admission to the trial. The dosage could be increased to two capsules per day after two weeks if required. If blood pressure remained high after one month, methyldopa tablets (500 mg.) could be added to the active treatment group, but placebo tablets were also added, starting with one-half tablet per day and increasing eventually to four tablets to maximize the double-blind nature of the trial. Patients remained in the double-blind portion of this trial until the summer of 1984 unless they were lost to followup, had an interruption of more than three months, or developed a mortal or morbid event as defined by the protocol: death, non-fatal cerebral or subarachnoid hemorrhage, development of grade III or IV retinopathy, dissecting aneurysm, congestive heart failure (not controllable without diuretics or antihypertensive agents), hypertensive encephalopathy, severe increase in left ventricular hypertrophy, or a severe rise in blood pressure exceeding defined limits.

During the double-blind portion of the trial, blood pressure was lower ($p<0.001$) in the actively treated patients than in those on placebo.(Table 6) At the end of the double-blind portion of the trial in the active treatment group, four percent were not receiving a diuretic, 51% took a diuretic but less than two capsules every day, and 45% took two or more capsules per day. Methyldopa was not required in 65% of the group whereas 26% were taking between one-half and two tablets a day, and only 9% required more than two tablets a day. The duration of the "intention to treat analysis" (double-blind period plus subsequent followup) was the same in both groups (4.69 years in the active treatment group vs. 4.63 years in the placebo group), but because more patients in the placebo group experienced a trial end-point, the duration of their followup within the double-blind portion of the study was shorter (2.99 years) compared to the actively treated group (3.36 years).

Table 6-EXPERIENCE DURING DOUBLE-BLIND PART OF TRIAL

Time	SBP/DBP $\bar{x}\pm$SD (n)		p
	Placebo	Active	
Randomisation	182±16 / 101± 7 (424)	183±17 / 101± 7 (416)	0·65 / 0·98
After 1 yr	172±23 / 95±12 (287)	151±17 / 88± 9 (300)	<0·001
3 yr	172±25 / 94±11 (171)	149±16 / 85± 9 (187)	<0·001
5 yr	171±25 / 95± 9 (93)	150±20 / 85± 9 (108)	<0·001
7 yr	167±22 / 90± 9 (27)	148±18 / 85±10 (39)	<0·001

SBP = sitting systolic blood pressure in mm Hg; DBP = sitting diastolic blood pressure in mm Hg.

The mortality rate from the intention-to-treat analysis revealed a non-significant change in mortality rate (-9%, p=0.41) but a significant reduction in cardiovascular mortality rate (-27%, p=0.037) primarily due to a reduction in cardiac and cerebrovascular mortality. In the double-blind portion of the trial, the cardiovascular mortality was reduced in the actively treated group even more (-38%, p=0.023) again primarily because of a reduction in cardiac deaths, cerebrovascular mortality, and death from myocardial infarction.(Table 7) In total, study terminating morbid, non-fatal cardiovascular events were significantly reduced by active treatment (-60%, p=0.064).(Table 8) The incidence of cardiovascular trial-terming events including deaths and morbid events can be appreciated in Figure 5. In the patients randomized to active treatment, there were 29 fewer cardiovascular events and 14 fewer cardiovascular deaths per 1,000 patient years during the double-blind portion of the trial.

Table 7-TERMINATING FATAL EVENTS ON RANDOMISED TREATMENT

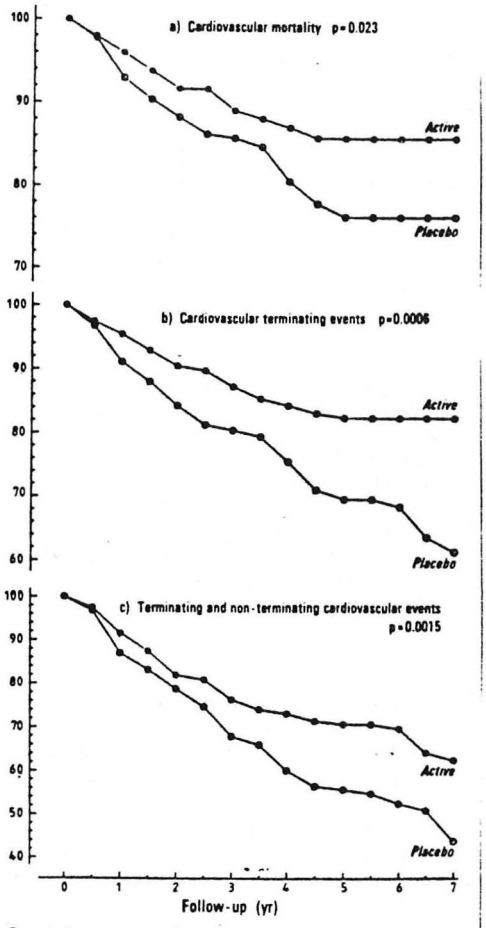
–	Placebo group		Active group		Percentage change† for active treatment		
	No of patients	Rate*	No of patients	Rate*	Mean	95% confidence limits	p‡
All causes	89	70	73	52	−26	−45 to +1	0·077
Non-cardiovascular, non-renal (total)	28	22	30	21	−3	−42 to +62	0·96
Cardiovascular (total)	61	48	42	30	−38	−58 to −8	0·023
Cerebrovascular	19	15	12	9	−43	−72 to +18	0·15
Cardiac (total)	29	23	17	12	−47	−71 to −3	0·048
Myocardial infarction	16	13	7	5	−60	−84 to −4	0·043
Others (including sudden death)	13	10	10	7	−30	−69 to +59	0·44
Pulmonary embolism and/or infarction	7	6	8	6	NC	NC	NC
Others	6	5	5	4	NC	NC	NC
Renal	0	0	1	1	NC	NC	NC

*Rates are number of patients having an event per 1000 patient years under observation.
†Percentage change is calculated from the rates, placebo rate = 100%.
‡Comparison of both treatment groups with Mantel-Cox statistics from life-table analysis.
NC = not calculated, since the rate in the placebo group was less than 10.

Table 8 –TERMINATING NON-FATAL CARDIOVASCULAR AND RENAL EVENTS ON RANDOMISED TREATMENT

–	Placebo group		Active group		Percentage change† for active group		
	No of patients	Rate*	No of patients	Rate*	Mean	95% confidence limits	p‡
Non-fatal, morbid cardiovascular terminating events							
Total	25	20	11	8	−60	−88 to −19	0·0064
Cerebral haemorrhage	3	2	4	3	NC	NC	NC
Papilloedema, retinal haemorrhages or exudates	5	4	0	0	NC	NC	NC
Severe congestive heart failure (not controlled by digitalis alone)	17	13	7	5	−63	−85 to −10	0·014
Non-fatal, non-morbid cardiovascular terminating events							
Total	30	24	10	7	−70	−85 to −38	0·0006
Severe increase in BP	19	15	2	1	−90	−98 to −59	0·0001
Therapy required with: Beta-blocker	10	8	6	4	NC	NC	NC
Calcium antagonist	0	0	1	1	NC	NC	NC
Diuretics	0	0	1	1	NC	NC	NC
Severe left ventricular hypertrophy or dilatation	1	1	0	0	NC	NC	NC
Renal: severe increase in creatinine	1	1	4	3	NC	NC	NC

*,†,‡For explanation of symbols, see table III.
NC = not calculated.



Cumulative percentage of survivors without events calculated for the patients on randomised treatment by life-table method."

Cardiovascular trial-terminating events include deaths and morbid events (group A of table IV). Cardiovascular non-terminating events are defined in table VI.

Figure 5.

The main benefits of this study were: 1) a reduction in fatal myocardial infarction, but not in non-fatal myocardial infarction, an improved case-fatality rate; 2) a prevention of severe, but not mild congestive heart failure; and 3) a reduction in the incidence of stroke. Non-cardiovascular mortality was not affected by the trial design or by active treatment. Adverse effects of therapy were considered minor.

Like the Veteran's Administration Cooperative Study(17), the EWPHPE Study(36) should put to rest questions concerning the value of treating diastolic hypertension (or diastolic plus disproportionate systolic hypertension) in the elderly. For balance sake, however, several studies do question the wisdom of therapy in this population. In 1970, Carter(37) reported a randomized trial of antihypertensive therapy in hypertensive stroke survivors. In patients under age 65, mortality and stroke recurrence were significantly reduced by treatment; elderly patients, however, realized no improvement in prognosis. In addition, the Hypertension-Stroke Cooperative Study Group(38) followed 452 hypertensive stroke survivors, half treated and half untreated, and found no protection against stroke recurrence with treatment.

Morgan and co-workers(39) studied 172 male patients, 53 to 78 years of age with diastolic pressures between 95 and 109 mmHg randomized to no treatment, dietary advice alone, a thiazide diuretic only, or beta blocker monotherapy. Although their results have not been reproduced in larger trials, an excess mortality rate from myocardial infarction was experienced in the thiazide diuretic group. Sprackling and co-workers(40) found no difference in survival for 123 infirm, institutionalized elderly (average age 80) patients with mild hypertension randomized to simple observation or treatment with methyldopa. The methodology of this study has been criticized, but the possibility that mild hypertension ceases to be a risk factor in the "extreme-old" deserves further study.

Perhaps the most important unresolved question from the EWPHPE(36) relates to the efficacy, safety and benefits of treating isolated systolic hypertension (ISH) now that the prevalence and associated risks in the elderly are better known(41). More than 3 million persons over the age of 60 are believed to have ISH.(42) Since the prevalence of ISH increases from 8% in the 60 to 69 year age group to 20% in the over 80 year age group, and with the "old-old" and "extreme-old" subpopulations being the fastest growing portion of our total population, the scientific addressment of this clinically controversial area is critical.

The Systolic Hypertension in the Elderly Program (SHEP) began its formal planning phase in July, 1980. A pilot was undertaken in 1983 to develop and test critical components of a larger full scale trial to be directed at the health consequence of treating ISH in the elderly.(41) The pilot enrolled 551 participants who were randomly assigned to treatment or placebo groups on a 4:1 ratio, respectively. The mean followup has been two years and a manuscript reporting on 12 months of followup is being circulated for publication. Currently, the only published report from the SHEP is a three month followup.(43) The authors reported a high rate of compliance with medication and clinic visits in these older volunteers. They also reported that 75% of those patients randomized to treatment on chlorthalidone alone (12.5 to 25 mg.) had achieved a goal systolic pressure (lower than 160 mmHg or 20 mmHg lower than admission level) compared to 34% in the placebo group. Atenolol or reserpine, drugs with a once per day dosing schedule, have been chosen as step two alternatives. From the preliminary report, it would seem that the systolic pressure component in elderly patients with ISH is more responsive to antihypertensive medications than the disastolic pressure "floor." The authors caution, nonetheless, that a gradual reduction in blood pressure, allowing time for desirable adaptive responses, is a more prudent course to follow in the elderly.

Until the SHEP study is published, the risk of treatment for ISH in the elderly must be weighed against the perceived benefit for the individual patient.(44)

Physiological Effects of Aging and the Pathophysiology of Hypertension in the Elderly

(Is Hypertension in the Elderly Different? If So, How?)

The aging process involves significant changes in various organ systems that influence the diagnosis, development and expression of hypertension and its complications. These changes may adversely affect cardiac function, tissue blood flow, circulatory responsiveness, and the metabolism and/or elimination of antihypertensive drugs. Rational pharmacological treatment depends upon an understanding of the interplay between the aging process and the pathophysiology of hypertension.(45, 46)

Blood pressure rises with age in industrialized nations, but in many non-industrialized populations, no significant increase in blood pressure occurs with age.(47, 48) Diet and other environmental factors probably account for the low incidence of hypertension in these cultures. Even in this society, many elderly persons remain normotensive, and as a result, exhibit a lower incidence of cardiovascular morbidity and mortality.(8) Hypertension is not a normal part of aging.

Vascular Changes with Aging

Arterial blood pressure is dependent upon the product of cardiac output times total peripheral resistance (BP=CO x TPR). In younger hypertensives, the hemodynamic pattern is characterized initially by a high (or normal) CO and a relatively normal TPR progressing over time to a higher TPR. Cardiac output stablizes or actually declines with age, and increased TPR accounts for the progressive rise in diastolic and systolic blood pressure with age.(49, 50) The increased rigidity of the aorta and peripheral arteries that accompanies aging is caused by loss of elastic fibers, deposition of collagen and calcium in the media, and thickening and atheromatous changes in the intima.(51) In contrast to the young person with an elastic aorta and large arteries that absorb some of the peak systolic volume arising during left ventricular systole, the more rigid inelastic aorta behaves more like a garden hose, transmitting the pulse generated during left ventricular systole relatively unchanged (diminished arterial compliance and capacitance), followed by a reduced diastolic recoil. An exaggerated pressure occurs for any given volume.(3)(Figure 6) These changes account for the disproportionate rise in systolic pressure in the elderly. Hyaline thickening may also occur in the arterioles of certain organs, contributing to further increases in TPR.(52)

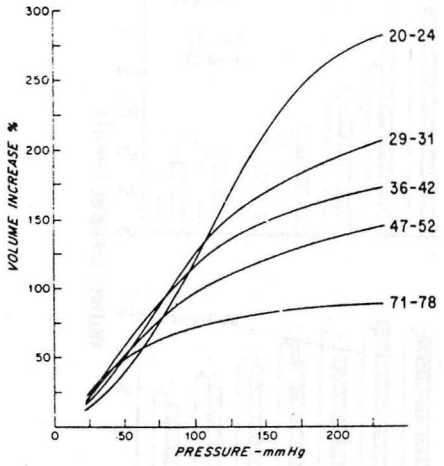


Figure 6 Influence of age on pressure-volume relation of human aortas obtained at autopsy. Age in years indicated on each curve. (Reproduced with permission of Jan Koch-Weser, M.D., and the American Journal of Cardiology.)

Recently, Avolio, et al(53) studied the effects of aging on changing arterial compliance and left ventricular load in a population where atherosclerosis is known to be rare (Beijing, Northern China). Arterial pulse wave velocity (PWV) in m/sec as measured by a transcutaneous Doppler technique was utilized in 480 normal subjects, age range 3 to 89 years. PWV is known to provide a suitable non-invasive index of left ventricular load and systemic arterial distensibility.(54) PWV (m/sec) is directly related to arterial wall stiffness and to wall thickness.(55)

In this study population, systolic and diastolic blood pressure increased with age.(Figure 7) PWV (m/sec) increased with age(Figure 8) and with increasing blood pressure.(Figure 9) Compared with that of Western populations, serum cholesterol tended to be lower, systolic pressure higher at ages over 35 years, and PWV (m/sec) higher at all ages. These results indicate that aging, and not concommitant atherosclerosis is the dominant factor associated with reduced arterial compliance and increased left ventricular load in the elderly. A number of other studies (56, 57) have been conducted in Occidental populations where atherosclerosis may have also contributed, but found essentially the same correlation between blood pressure, aging, and PWV (m/sec).(Figure 10) The loss of vessel elasticity associated with aging blunts the responsiveness of aortic and carotid sinus baroreceptors to changes in blood pressure.(58)

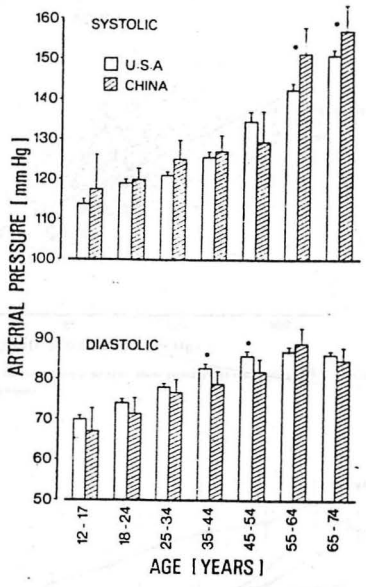


FIGURE 7 Comparison of systolic and diastolic blood pressure between Chinese subjects (this study) and U.S. subjects (ref. 41). The U.S. data are for sitting blood pressure, while the Chinese data are for supine recordings. Values are mean ± 2 SEM. In groups marked with an asterisk, mean values between U.S. and China data are significantly different ($p < .05$).

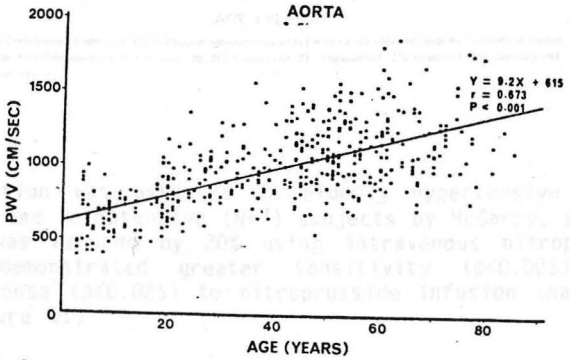


FIGURE 8 Aortic PWV, measured between base of the neck and groin for all subjects (both male and female subjects) between ages 3 and 89 years. Individual values were determined as the average of 10 pairs of pulses simultaneously recorded with identical transcutaneous Doppler transducers.

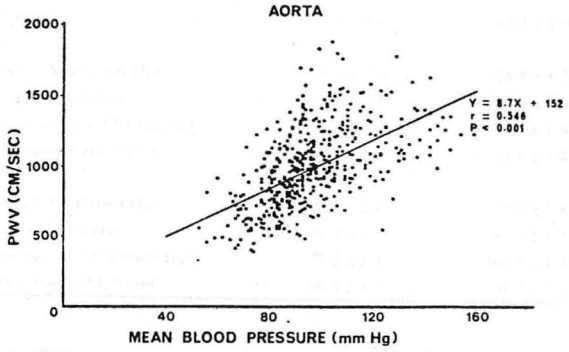


FIGURE 9 Aortic PWV and mean pressure for all subjects at all ages. Mean pressure was calculated as: $\overline{BP}$ = ⅓ (systolic − diastolic) + diastolic BP = supine blood pressure.

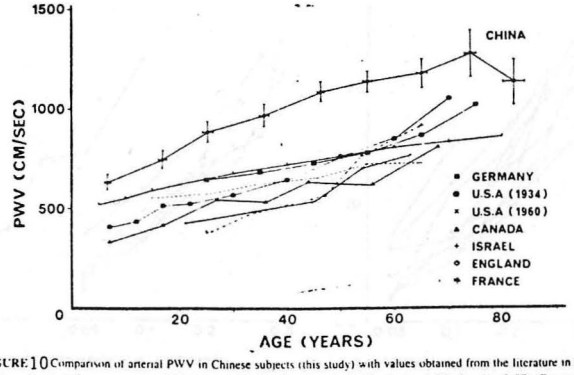


FIGURE 10 Comparison of arterial PWV in Chinese subjects (this study) with values obtained from the literature in studies conducted in the following countries: U.S.A. (refs. 20, 21), Canada (ref. 23), England (ref. 22), Israel (ref. 27), Germany (ref. 26), and France (ref. 12).

Baroreflex function was assessed in elderly hypertensive (N=10), young hypertensive (N=10) and normotensive (N=7) subjects by McGarry, et al.(59) Mean arterial pressure was reduced by 20% using intravenous nitroprusside. The elderly subjects demonstrated greater sensitivity ($p<0.005$) and greater variability of response ($p<0.025$) to nitroprusside infusion than either young group.(Table 9)(Figure 11)

TABLE 9 *Mean Arterial Pressure (MAP) and Heart Rate (HR) Supine and Standing Before and After Nitroprusside Infusion*

	Young normotensives	Young hypertensives	Old hypertensives
No.	7	10	10
Age (yrs)	35 ± 4.6	45.5 ± 2.9	71.2 ± 1.8
Supine			
Baseline MAP (mm Hg)	98.1 ± 1.9	125.8 ± 3.3	132 ± 6.4
Baseline HR (bpm)	75.6 ± 2.4	78.9 ± 1.9	74.9 ± 2.9
Nitroprusside MAP (mm Hg)	76.1 ± 1.4	98.6 ± 1.9	99.9 ± 5.0
Nitroprusside HR (bpm)	80.9 ± 2.6	81.8 ± 3.4	77.5 ± 3.2
Standing			
Baseline MAP (mm Hg)	98.7 ± 2.4	127.5 ± 2.8	130.5 ± 5.4
Baseline HR (bpm)	81.4 ± 2.5	85.8 ± 1.7	77.3 ± 2.9
Nitroprusside MAP (mm Hg)	77.5 ± 2.1	100.5 ± 2.4	99.6 ± 3.9
Nitroprusside HR (bpm)	96.1 ± 3.3	98.7 ± 3.0	84.3 ± 3.6

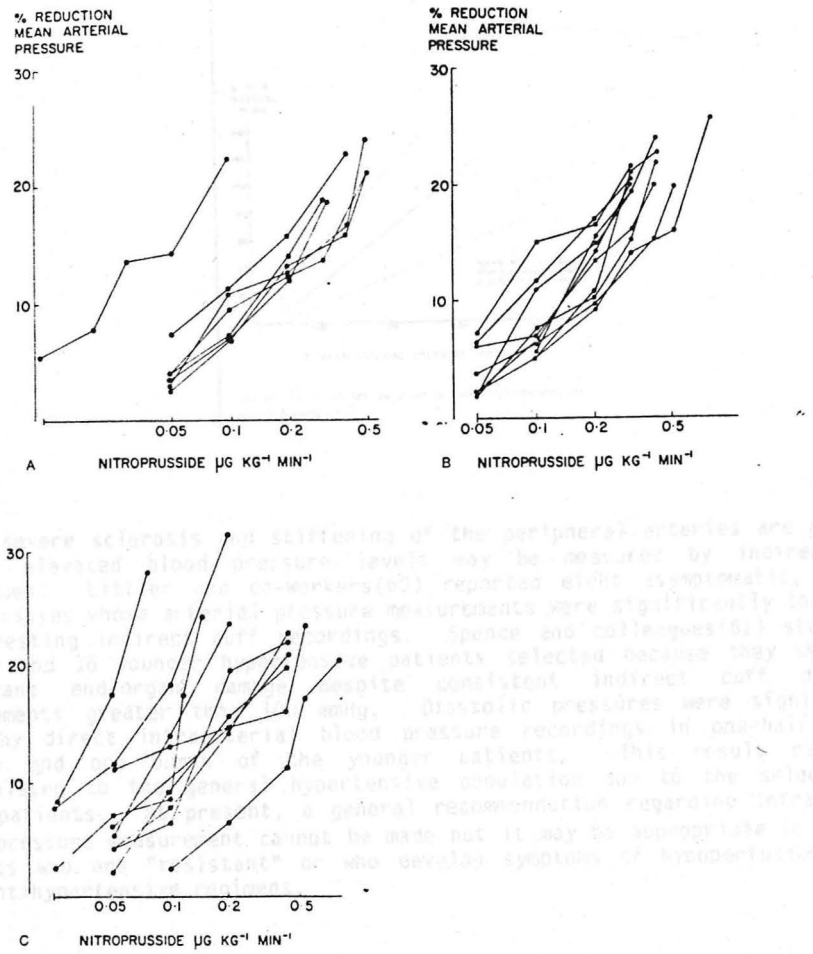


FIGURE 11 *Log dose blood pressure response curves to nitroprusside in the erect position. A. Seven young normotensive subjects. B. Ten young hypertensive subjects. C. Ten elderly hypertensive subjects.*

Tnere were no significant differences between the three groups in the slight increase in heart rate in the supine position. However, in the upright standing position, heart rate increases were significantly less in the elderly hypertensives than in the young hypertensive group ($p<0.01$) or the young normotensive group ($p<0.005$). The slope of the regression line relating change in blood pressure with change in R-R interval was also less for the elderly patients.(Figure 12) Insensitive baroreceptors impair the compensatory and vasoconstrictive response to posture or to drug-induced blood pressure reductions in the elderly.

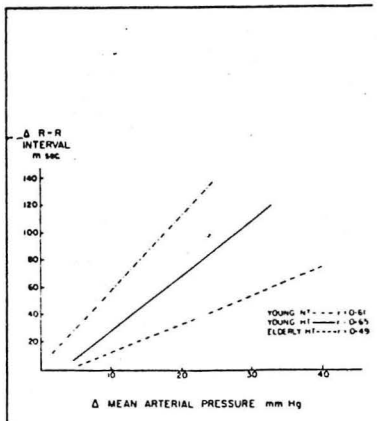


FIGURE 12 *Baroreflex sensitivity in young hypertensives and elderly hypertensives.*

If severe sclerosis and stiffening of the peripheral arteries are present, falsely elevated blood pressure levels may be measured by indirect cuff techniques. Littler and co-workers(60) reported eight asymptomatic, treated hypertensives whose arterial pressure measurements were significantly lower than their resting indirect cuff recordings. Spence and colleagues(61) studied 24 elderly and 16 younger hypertensive patients selected because they showed no signficant end-organ damage despite consistent indirect cuff diastolic measurements greater than 100 mmHg. Diastolic pressures were significantly lower by direct intraarterial blood pressure recordings in one-half of the elderly and one-fourth of the younger patients. This result cannot be extrapolated to the general hypertensive population due to the selection of these patients. At present, a general recommendation regarding intraarterial blood pressure measurement cannot be made but it may be appropriate in selected patients who are "resistant" or who develop symptoms of hypoperfusion on low dose antihypertensive regimens.

A simple bedside diagnostic procedure, the so-called "Osler's Maneuver" has recently been described to help differentiate patients with true hypertension from those with "pseudohypertension."(62) The maneuver is performed by assessing the palpability of the pulseless radial or brachial artery distal to a point of occulsion of the artery manually or by cuff pressure. Arteries that remain clearly palpable are termed Osler-positive in contrast to a collapsed, non-palpable artery (Osler-negative). These authors classified 24 elderly hypertensive patients according to this maneuver (N=13, Osler-positive, N=11, Osler-negative), and then measured intraarterial pressure, arterial compliance and systemic hemodynamics. Clinical and laboratory findings were similar in both groups, except that Osler-positive patients had a higher cholesterol level.(Table 10) The Osler-positive patients had falsely elevated blood pressures with a 10 to 54 mmHg difference between indirect cuff and intraarterial pressure.(Table 11)

Table10 Clinical and Laboratory Findings in 13 Osler-Positive and 11 Osler-Negative Patients with Hypertension.*

	Osler-Positive	Osler-Negative
	mean ±S.D.	
Age (yr)	77.6±5.9	74.8±7.0
Race (B/W)	2/11	1/10
Sex (M/F)	7/6	1/10
Weight (kg)	63.7±9.3	68.9±12
Height (cm)	162.1±9.3	161.1±6.6
Body-surface area (mg/m^2)	1.7±0.2	1.7±0.1
Plasma potassium (mmol/liter)	4.3±0.5	4.3±0.5
Plasma sodium (mmol/liter)	141.9±3.1	143.2±2.6
Creatinine (mg/100 ml)	1.14±0.2	1.05±0.5
Cholesterol (mg/100 ml)	267±46	219±35 †
Glucose (mg/100 ml)	114.4±21.5	102.5±11.6

*To change creatinine values to micromoles per liter, multiply by 88.40; to change cholesterol values to millimoles per liter, multiply by 0.02586; and to change glucose values to millimoles per liter, multiply by 0.05551.

†P<0.05.

Table11 Arterial Pressures in 13 Osler-Positive and 11 Osler-Negative Patients with Hypertension.

	Osler-Positive	Osler-Negative
	mean ±S.D.	
Intraarterial pressure (mm Hg)		
Systolic	180.5±24.4	172.9±26.1
Diastolic	77.9±11.2	74.5±9.6
Mean arterial	112.1±14.1	107.3±14.5
Cuff pressure (mm Hg)		
Systolic	196.4±22.2	169.9±25.4 *
Diastolic	94.3±11.0	79.8±11.2 †
Mean arterial	128.3±13.5	109.6±13.8 †
Difference between the two (mm Hg)		
Systolic	15.8±14.2	−3.0±4.8 ‡
Diastolic	16.4±8.0	5.3±6.0 †
Mean arterial	16.2±8.3	2.6±4.2 ‡

*P<0.05.

†P<0.01 as compared with Osler-positive patients.

‡P<0.001.

With the exception of systolic pressure in two patients, cuff pressures were consistently higher than intraarterial pressures by Osler-positive subjects.(Figure 13) Arterial compliance as measured by PWV (m/sec) in these patients correlated with the difference between indirect cuff and intraarterial pressures demonstrating that the stiffer the artery the more pronounced the pseudohypertension. This study would suggest that PWV (m/sec) may be helpful in diagnosing pseudohypertension.(Table 12) The arterial changes related to aging are summarized in Table 13.

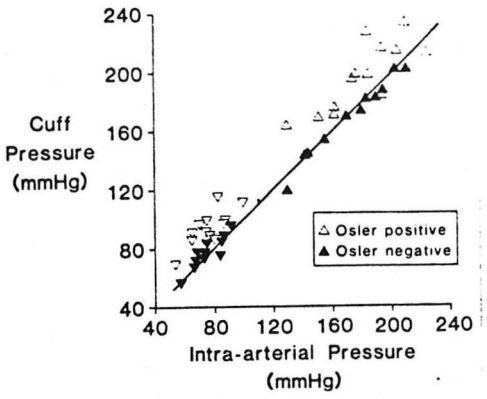


Fig. 13 Comparison between Cuff and Intraarterial Systolic (△) and Diastolic (▽) Pressures in Osler-Positive (Open Symbols) and Osler-Negative (Closed Symbols) Patients.

With the exception of the systolic pressures in two patients, cuff pressures were consistently higher than intraarterial pressures in Osler-positive subjects.

Table 12 Systemic Hemodynamic Findings and Indexes of Arterial Compliance in 13 Osler-Positive and 11 Osler-Negative Patients with Hypertension.

	Osler-Positive	Osler-Negative
	mean ±S.D.	
Heart rate (bpm)	80.2±14.9	79.1±11.9
Cardiac output (liters/min)	5.2±1.5	5.6±1.3
Cardiac index (liters/min/m²)	3.1±0.7	3.3±0.7
Stroke volume (ml)	65.9±19.1	72.2±15.8
Total peripheral resistance (U)	23.7±8.5	22.1±9.1
Mean left ventricular ejection rate (U)	209.3±60.1	212.6±55.8
Left ventricular stroke work (U)	156.4±40.9	153.0±40.7
Plasma volume (ml)	2802.7±669.2	2498.0±575.8
Pulse-wave velocity (m/sec)	12.7±4.0	8.1±1.5 *
Diastolic-pressure decay (ml/mm Hg)	1.6±0.6	2.0±0.8 †

*P<0.01
†P<0.01 as compared with Osler-positive patients.

Table 13 **Arterial Changes Related to Aging**

Increased calcium and collagen
Reduced elasticity and compliance
Increased pulse pressure
Decreased baroreceptor sensitivity
Hyaline thickening in arterioles, small arteries
Increased peripheral resistance

Cardiac Changes with Aging

The cardiac changes related to aging are summarized in Table 14. Hemodynamic studies in healthy, as well as hypertensive persons, indicate that aging usually results in a normal or slowed heart rate, a decreased left ventricular ejection rate, a 10 to 30% reduction in cardiac output [65 year olds compared to 25 year olds(50)], and increased left ventricular wall thickness. This latter change represents concentric hypertrophy and occurs most likely in response to increased peripheral resistance and reduced compliance of the large vessels which increases impedence to left ventricular ejection and markedly increases the workload of the heart. As previously mentioned, left ventricular hypertrophy may lead to deterioration of ventricular function, and particularly in the face of untreated hypertension, is associated with a much higher (10X) likelihood of congestive heart failure.(26) Several echocardiographic studies, performed in humans, strongly support the association between aging and the development of left ventricular hypertrophy.(63, 64) Obviously, the increase in cardiac work could also exacerbate coronary artery disease.

Table 14 **Cardiac Changes Related to Aging**

Increased left ventricular afterload
Decreased cardiac output—rest and exercise
Reduced maximal exercise capacity
Decreased heart rate
Decreased left ventricular ejection fraction
Decreased stroke volume
Reduced myocardial responsiveness to catecholamines
Prolonged contraction time to peak tension

The decrease in cardiac output with aging occurs both at rest and with exercise.(65, 66) This reduction with exercise is associated with decreases in oxygen uptake, maximal heart rate response and a demonstrable decrease in left ventricular (LV) contractile performance characterized by decreased LV ejection fraction and stroke volume.(67) This latter decline appears to be markedly influenced by the degree of impedence to ejection or afterload, and hence to systolic blood pressure.(68) Schocken, et al(69) recently found that the exercise-induced decrease in LV ejection fraction and increase in LV end-systolic volume index remained unaltered by training. They examined 24 normal elderly persons (mean age 72.0 years) before and after a 12 week program of physical training with radionuclide angiocardiography. These subjects did achieve training effects as measured by increased functional capacity and decreased double product at one-half the maximum workload initially attained. A significant increase occurred after training in the cardiac output ($p<0.02$) and the augmentation of the end-diastolic volume index ($p<0.05$) in response to exercise. The achievement of overall training effects, without reversing the age-associated differences in LV contractile performance, suggests that deconditioning is not a significant contributor to the decline in LV function seen with aging.

A number of other cardiac changes occur with aging, but can also be seen in certain other disease states. There may be an increase in myocardial stiffness due to increased deposition of collagen and amyloid fibrils,(70) and a lengthening of the period of systolic contraction.(71) Sinus node dysfunction can also be problematic for elderly patients with impaired baroreceptor function. Such patients are prone to significant bradyarrhythmias when given sympatholytic agents.(72)

Humoral Responses to Aging

The responsiveness of the heart to catecholamine stimulation appears to be imparied(73) and has been attributed to a decrease in number or affinity of myocardial adrenoreceptors.(74, 75) A recent study to evaluate the molecular basis for reduced catecholamine responsiveness in the elderly found that, as compared to young subjects with a three-fold increase in plasma cyclic AMP levels in older adults (mean age 77 years) had only a one and one-half fold rise after salbutamol infusion.(76)(Figure 14) There was an increase in pulse rate, systolic blood pressure and a decrease in diastolic blood pressure in the young compared to the older participants. This study suggests that a defect in the peripheral beta-receptor linked adenylate cyclase complex is present in the elderly.

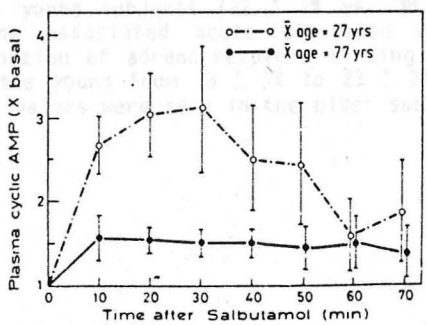


Fig. 14 The effect of salbutamol infusion on plasma cyclic AMP levels in two age groups. Values are mean (± SEM) multiples of basal cyclic AMP levels.

Another possible explanation of the decreased beta adrenoreceptor responsiveness is a compensatory down-regulation because of high circulating catecholamine levels. The relation between adrenoreceptor affinity for agonists and age in beta-adrenoreceptors on lymphocytes was investigated in 20 healthy men (age 21 to 74 years old) by determining the concentration of isoproterenol required to inhibit 50 percent of iodo-hydroxybenzylpindolol binding in vitro (IC_{50}).(77) An increase in IC_{50}, which represents a reduction in affinity, was seen with increasing age(Figure 15) and plasma norepinephrine concentration. Six of the younger subjects (age 21 to 29 years) and six of the older subjects (age 55 to 74 years) were also studied in both the supine and upright positions.

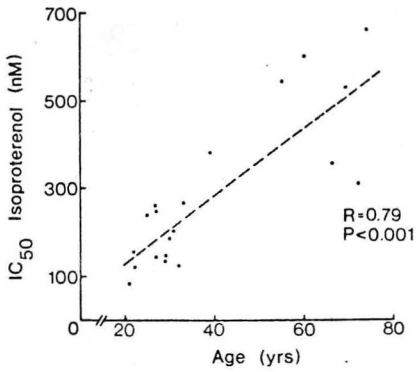


Fig. 15 Correlation between Lymphocyte β-Receptor Affinity for Agonist (as Represented by IC_{50} Isoproterenol for [^{125}I]Iodohydroxybenzylpindolol Binding) and Age. Note that an increase in IC_{50} represents a reduction in affinity.

In both positions the elderly had higher catecholamine levels than the young.(Figure 16) In samples obtained in the supine position, the proportion of adrenoreceptors binding agonist with a high affinity decreased in the older subjects compared to the young subjects (22 $\pm$ 1% vs. 38 $\pm$ 3% $p<0.05$). With upright position and the associated acute elevation of endogenous plasma catecholamines, the proportion of adrenoreceptors binding agonists with a high affinity was reduced in the young from 38 $\pm$ 3% to 23 $\pm$ 3% ($p<0.005$), while no reduction from the supine values were seen in the older subjects.(Figure 17)

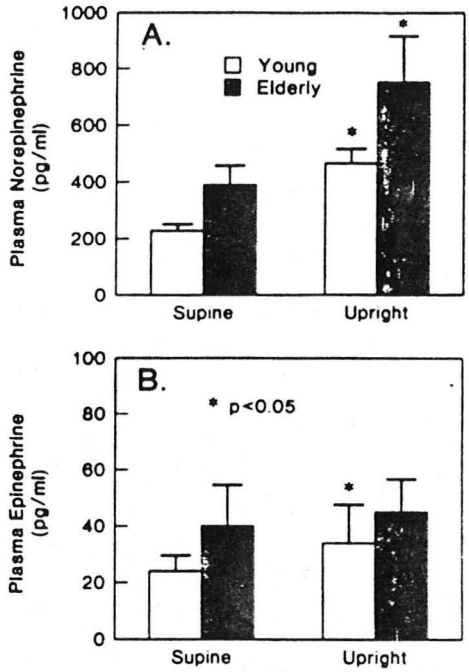


Fig. 16 Effect of Posture on Plasma Catecholamine Levels in Young and Elderly Subjects.
Asterisk denotes significant difference between level in supine subjects and level in upright subjects ($P<0.05$).

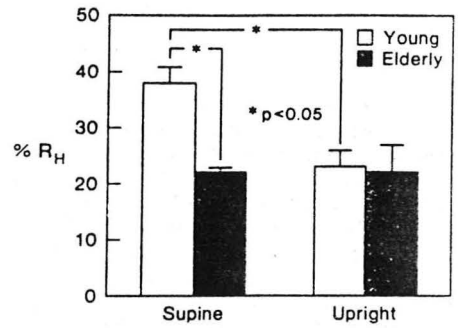


Fig. 17 Effect of Posture on Proportion of Receptors Binding Agonist with a High Affinity (%R_H).
The % R_H was significantly lower in samples from supine elderly subjects as compared with young subjects. With upright posture, % R_H was reduced in young subjects, but was unchanged in elderly subjects.

Tnis study demonstrates that a reduced proportion of leukocyte beta-adrenoreceptors bind agonist with high affinity in the elderly. This reduction suggests a decrease in the coupling efficiency between the adrenoreceptor and the catecholamine - moiety in the elderly. Despite adrenoreceptor changes, enhanced sympathetic nervous system tonicity appears to be an important factor in the cause and maintenance of diastolic and disproprotionate systolic hypertension.(78)

Plasma renin activity decreases progressively with age in both normotensive and hypertensive subjects.(79) Recently, Gavras, et al(80) studied 247 ambulatory hypertensive patients, and 45% over the age of 40 years had low renin activity, compared to only 2% of patients less than 40 years.(Table 15)

Table 15 **Humoral Characteristics of Young Versus Old Patients With Essential Hypertension**

Young (<40 yr)	Old (<60 yr)
Low PRA 2%	Low PRA 48%
High PRA 14%	High PRA 2%
Normal plasma aldosterone	Normal plasma aldosterone
Greater increments of PRA and plasma aldosterone post furosemide	Lesser increments of PRA and plasma aldosterone post furosemide
Lower plasma norepinephrine	Higher plasma norepinephrine

Adapted from Gavras et al.
PRA = plasma renin activity.

In contrast, high plasma renin in the elderly is uncommon and may indicate a secondary form of hypertension associated with renovascular disease.(81) Changes in plasma renin levels in response to dietary sodium restriction or furosemide stimulation also diminish with aging. This change may be due to a physiologic response to elevated blood pressure, but in large part it is also due to a decreased functional activity of the juxtaglomerular apparatus of the kidney as a result of fibrotic changes or hyalinization of the arterioles. The incidence of renovascular hypertension in the elderly is not known, but it may be higher than in the general population due to the high prevalence of atherosclerosis affecting renal arteries. Recently, Laugesen(82) studied 127 hypertensive patients over age 50 (50% of subjects were over age 70) and found that the renin-angiotensin-aldosterone system and renovascular lesions played a pathogenic role in 10 to 15 percent of non-selected elderly hospitalized hypertensives. The practical consequences of his study however were few since only two patients underwent surgery and most certainly this was a skewed population (more often a 1 to 2% incidence of renovascular disease in the elderly is quoted). Before beginning an elaborate investigation for renovascular disease in the elderly, it is wise to consider the potential consequences for the individual patient. Age alone is not an important factor in determining the likelihood of a successful surgical treatment, but repair of arteriosclerotic lesions are less likely to be curative at any age compared to fibromuscular dysplasia. The results of percutaneous transluminal dilatation as an alternative to surgery in the management of elderly renovascular hypertensives has also been disappointing.(83) While the renin profile is seldom necessary in routine clinical practice, it can help predict the response to dietary sodium restriction(84)(Figure 18) or help direct pharmacological interventions (diuretics vs. adrenergic blockers) in elderly patients with isolated systolic hypertension, a condition that few think of as being driven by the renin-angiotensin-aldosterone system.(85)(Figure 19)

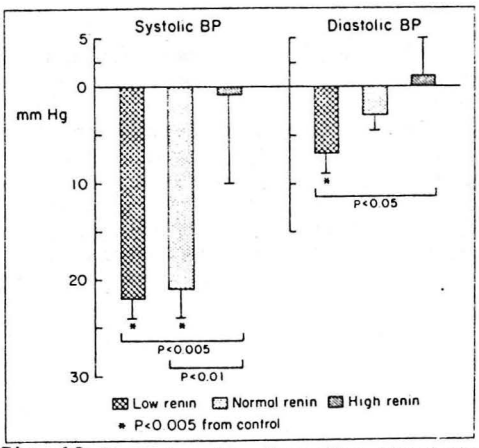


Fig. 18 *Comparison of the effects of low sodium intake on systolic and diastolic blood pressure in low-, normal-, and high-renin isolated systolic hypertension.*

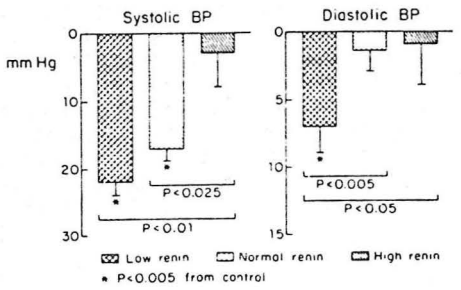


Fig. 19 Effect of diuretic therapy on systolic and diastolic blood pressure (BP) in low-, normal- and high-renin isolated systolic hypertension.

Aldosterone secretion also declines with advancing age. The mean and upper limit of the range of urinary aldosterone excretion were considerably lower in normal subjects over age 50, compared to normal subjects under age 30, during unrestricted sodium intake and after furosemide stimulation or a 20 M/eq sodium diet in a study by Hegstad, et al.(86)(Figure 20) This difference was only evident in the stimulated upright posture. The metabolic clearance of aldosterone was similar in young and old subjects.(Figure 21) Eight of the patients over age 40 had an aldosterone-producing adenoma and without adjusting for age, four of these would have had "normal" aldosterone excretion rates. The effect of age on aldosterone secretion should be considered during the evaluation of elderly hypertensives for primary aldosteronism.

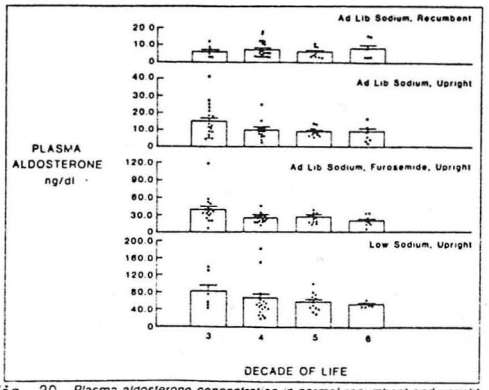


Fig. 20 *Plasma aldosterone concentration in normal recumbent and upright subjects while on an ad lib sodium diet, and after sodium depletion with furosemide or a 20 meq sodium diet. The* ***brackets*** *represent the SEM.*

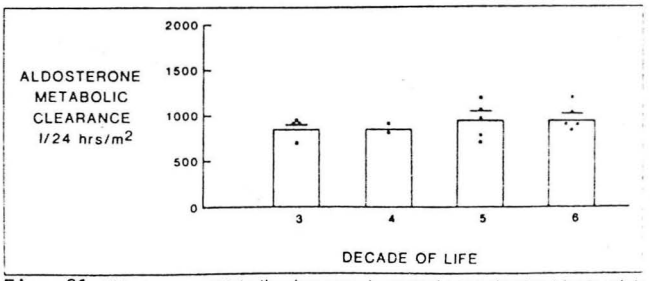


Fig. 21 *Aldosterone metabolic clearance in normal recumbent subjects while on an ad lib sodium diet. The* ***brackets*** *represent the SEM.*

In elderly normotensive subjects (age 60 to 90), plasma aldosterone concentration (PAC) showed a significant correlation with norepinephrine (NA) and dopamine (DA) 24 hour urinary excretion rates ($p<0.001$).(87)(Figure 22) Plasma renin activity also tended to correlate with urinary norephinephrine levels, but the degree was weak and not significant. Still there is little doubt concerning the interrelationship between the catecholamine and renin-angiotensin-aldosterone system. Stimulation of the intrarenal beta adrenoceptors by catecholamines increases renin secretion from the juxtaglomerular apparatus(88, 89), and angiotensin II stimulates catecholamine release from the sympathetic synapse.(90, 91)

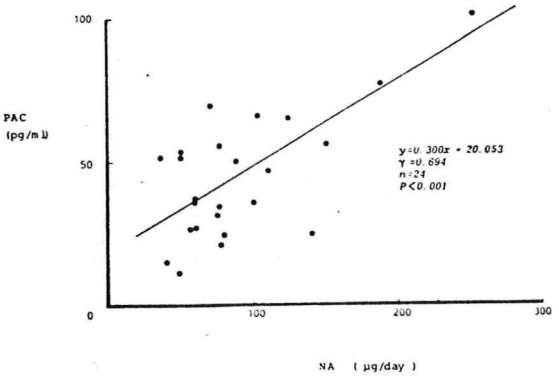


Fig. 22 Correlation between PAC and noradrenaline in the 24 hr-urine

Organ Blood Flow and Tissue Perfusion

Aging also effects cerebral physiology and function. In normotensives and hypertensives, aging is associated with a decrease in regional cerebral blood flow (CBF) and an increase in peripheral resistance.(92, 93) Mean gray matter CBF and mean gray cerebral metabolic rate for O_2 ($CMRO_2$) is depicted in Figure 23. Tnis data is derived from a study in 27 patients, free of any vascular risk factors or a history of cerebral disease (age 19 to 76 years). It utilized a non-invasive oxygen-15, continuous inhalation technique and positron emission tomography (PET) to measure CBF.(93) Mean gray matter CBF, but not mean gray matter $CMRO_2$, decreased linearly with age ($p<0.02$). However, when younger subjects ($\leq$ 50 years) were compared to older subjects (> 50 years), an age-related matched decrease in CBF and $CMRO_2$ was observed in mean gray matter (18% and 17% reduction, respectively, $p<0.05$)(Figure 24) White matter CBF and $CMRO_2$ remained remarkably stable with advancing age.

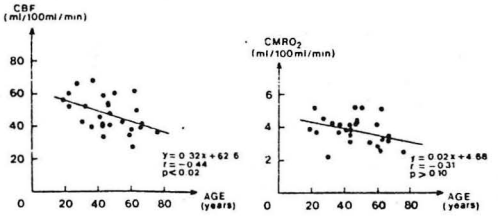


Fig. 23 *Plot of mean gray CBF and mean gray $CMRO_2$ values versus age in 27 control subjects. Significant linear relationship with age was found only for CBF ($p < 0.02$).*

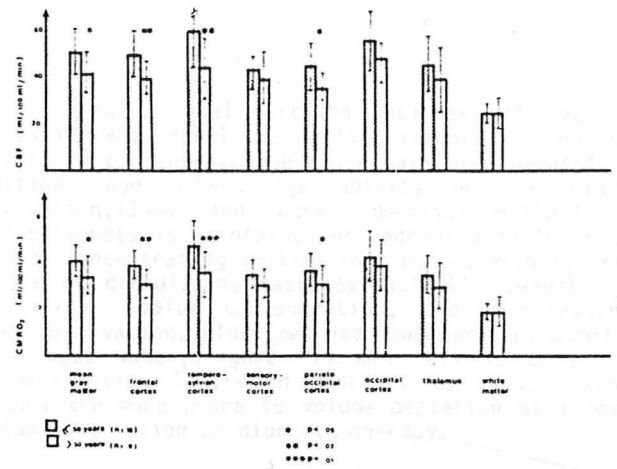


Fig. 24 *Regional patterns of CBF and $CMRO_2$ in young and aged subjects. Mean values and one standard deviation are indicated for each brain region studied.*

Although autoregulation of cerebral blood flow remains intact in most persons, the range over which constancy of flow is maintained is shifted toward higner pressures in hypertensive patients.(94)(Figure 25) Consequently, as blood pressure is lowered, symptoms or signs of poor cerebral perfusion may develop at higher mean arterial pressures than in normotensive persons. In addition, arterial stiffening and atherosclerosis may impair the ability of the arterioles to dilate in response to a fall in blood pressure in older people. Although the abnormalities in autoregulation are reversible, to some extent, with long-term control of blood pressure,(95) careful monitoring and gradual reduction of blood pressure are necessary to avoid cerebral hypoperfusion. The elderly patients with fixed arteriosclerotic lesions in the cerebrovascular circulation are obviously at high risk for such complications from rapid reduction in blood pressure.(96, 97)

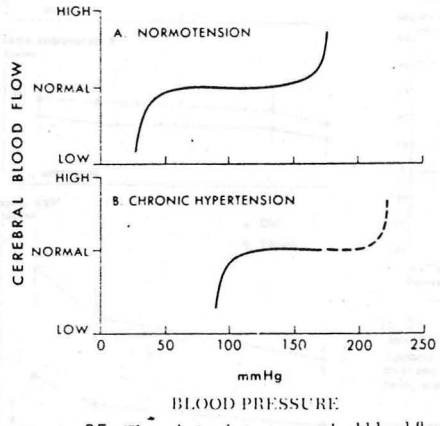


Figure 25 The relation between cerebral blood flow and mean arterial pressure in normotensive individuals (A) and in those with chronic hypertension (B). In these experiments, arterial pressure was altered rapidly with pharmacologic agents. The broken line indicates a hypothetical curve. (Courtesy of John J Caronna, M.D.)

As a rule, renal function declines with age. A decrease in glomerular filtration(98), renal blood flow, cortical blood flow(99), renal mass, and the ability to concentrate the urine have been demonstrated in elderly persons. In addition, age alters the ability of the kidney to respond to sodium deprivation,(100) and water deprivation.(101) Vasopressin osmoreceptor responsiveness is maintained or increased in the elderly so that the deficit in urinary concentrating ability that occurs with age reflects renal causes and not a lack of circulating vasopressin.(101) Despite greater increases in plasma osmolality, sodium concentration, and vasopressin levels,(Figure 26) after water deprivation, older men had lower urinary osmolality, are less thirsty, and drink less water,(Figure 27) and fail to dilute their plasma and urine to pre-deprivation levels in contrast to younger subjects.(Figure 28) Elderly persons are more prone to volume depletion as a result of these changes during sodium restriction or diuretic therapy.

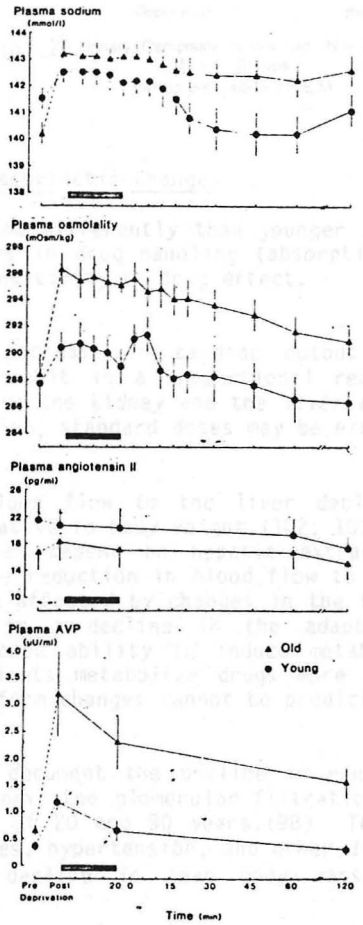


Fig. 26 Plasma Sodium Concentrations, Osmolality, Angiotensin II Concentrations, and Vasopressin (AVP) Concentrations in the Old (N = 7) and Young (N = 7) Groups.

Plasma vasopressin was measured in four subjects in the young group. Symbols represent mean values, and bars S.E.M. The hatched rectangle represents the single-blind sham infusion. To convert plasma vasopressin and angiotensin II concentrations to picomoles per liter, multiply by 2.0 and 0.97, respectively

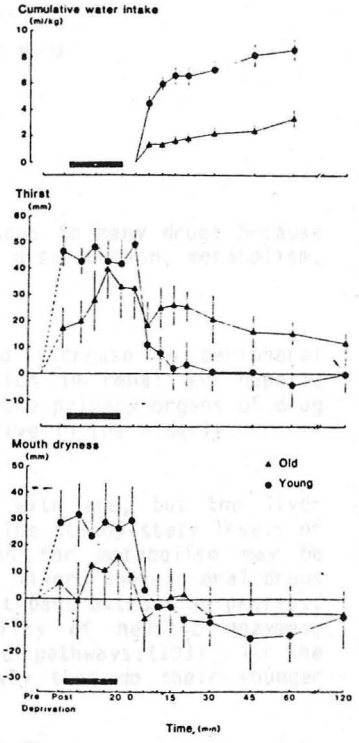


Fig. 27 Cumulative Water Intake and Changes in Thirst and Mouth Dryness in the Old (N = 7) and Young (N = 7) Groups. Symbols represent mean values, and bars S.E.M. Changes in thirst and mouth dryness were measured on a visual-analogue rating scale. The hatched rectangle represents the single-blind sham infusion.

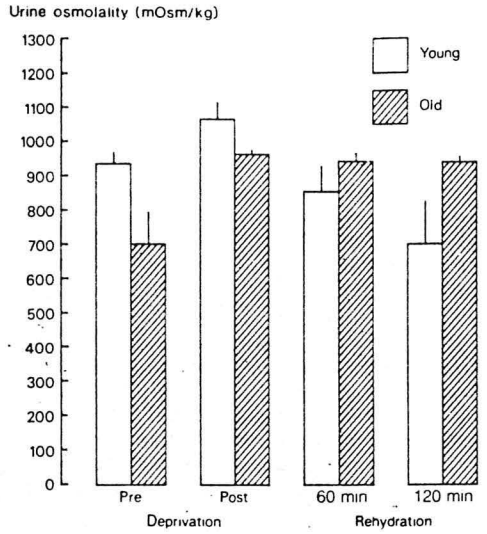


Fig. 28 Urinary Osmolality in the Old (N = 7) and Young (N = 7) Groups.
Values are means ±S.E.M.

Age-Related Pharmacokinetic Changes

The elderly respond differently than younger persons to many drugs because of age-related changes in drug handling (absorption, distribution, metabolism, and excretion) and sensitivity to drug effect.

The age-related decrease in cardiac output and increase in peripheral vascular resistance result in a proportional reduction in renal and hepatic blood flow.(102) Since the kidney and the liver are the primary organs of drug metabolism and excretion, standard doses may be excessive in the elderly.

Not only does blood flow to the liver decline with age, but the liver decreases in size relative to body weight.(102, 103) The steady-state levels of intravenous drugs that depend on hepatic extraction for metabolism may be altered because of the reduction in blood flow to the liver, whereas oral drugs are more likely to be affected by changes in the first-pass extraction process. Aging also results in a decline in the adaptability of hepatic enzymes, particularly a decreased ability to induce metabolic pathways.(103) On the average, elderly patients metabolize drugs more slowly than do their younger counterparts, but uniform changes cannot be predicted.

It is easier to document the decline in renal function that occurs with aging. In a normal man, the glomerular filtration rate declines an average of 35% between the ages of 20 and 90 years.(98) This loss of renal function is intensified by diabetes, hypertension, and other disease states. Still, because of the age-related decline in lean body mass, the endogenous creatinine

production declines, allowing the deterioration in renal function to be concealed by a "normal" serum creatinine level.(104) Cockroft and Gault(105) recommend the following formula for the estimation of creatinine clearance in elder men:

$$\frac{(140 - \text{age}) \times \text{body weight (kg)}}{72 \times \text{serum creatinine level}}$$

The product of this formula multiplied by 0.85 yields an estimate of renal function in elderly women. Both values are even more helpful when body weight is corrected for the reduction of lean body mass. The reason such formulas are necessary to determine renal function is highlighted by a study of octogenarian women.(106) Their serum creatinine levels were all below 1.5 mg/100 ml (averaging approximately 1.0 mg/100 ml), but their creatinine clearances were below 60 ml/min (averaging approximately 40 ml/min).

Several factors, such as a reduced splanchnic blood flow, an increased gastric pH, and a reduction in both active absorption and passive transport, would be expected to alter drug absorption in the aged gut.(107, 108, 109) In contrast, the elderly often have slowed gastrointestinal motility, which would theoretically result in enhanced absorption of some drugs.(107) Of all age-related pharmacological changes that affect antihypertensive therapy, those affecting absorption are the least important.(110)

In general, fat stores increase with age, whereas total body water, plasma volume, extracellular fluid, and lean body mass decrease.(111, 112) These changes in body composition, which are usually more pronounced in men than in women, can limit the volume of distribution of water-soluble drugs and increase the volume of distribution of fat-soluble drugs. In the first instance, a given dose of a water-soluble drug that distributes to total body water would be expected to yield higher peak serum levels in elderly than in young subjects.(113) "Standard" doses of such drugs could result in a greater potential for toxicity in the elderly.

The affinity of albumin or other plasma proteins for drugs is probably normal in the elderly. However, it is apparent that albumin concentration decreases with age.(114, 115) Standard doses of drugs that are avidly albumin-bound may result in more free drug being available for pharmacological action, but hopefully not toxic reaction. Multiple drug therapy would further increase the likelihood of excessive free drug and could result in an adverse drug interaction.(116)

Finally, tissue sensitivity to various hormones,(117) like the response to catecholamines (their analogs or antagonists) may be reduced. In some cases, such as with levothyroxine, elderly patients require much smaller doses for physiologic hormone replacement than young patients.(118) By the same token, the elderly seem to be sensitive to certain drugs, such as benzodiazepines,(119) even when a slightly slower metabolic clearance rate is taken into consideration.

Individualization of Antihypertensive Therapy in the Elderly

Elderly hypertensives have certain age-related biological, physiological, and pharmacological changes that should influence the physician's selection of antihypertensive drugs. These patients present complex and challenging management problems because they may have concurrent significant diagnoses and may use several medications simultaneously. Four of every five elderly persons have one or more chronic illnesses.(120) In one study,(121) hospitalized Medicare patients received an average of ten prescription drugs, and the ambulatory or institutionalized elderly often receive between 3 and 12 medications simultaneously.(122) Careful reviews of drug use in nursing home residents have revealed that many prescriptions are either inappropriate, ineffective, or likely to result in adverse drug interactions.(123-125) Certain drug categories are commonly represented in such reviews, including cardiovascular drugs (digitalis, diuretics, antihypertensives), analgesics, laxatives, and psychotropics (hypnotics, antianxiety agents, antidepressants, neuroleptics).(123, 126) Many elderly patients hoard drugs for later use, loan prescribed drugs to friends for similar symptoms, use a system of lay referral culminating in the purchase of multiple over-the-counter remedies, and they often store drugs in other than their original containers.(127) It is small wonder that elderly patients are at greater risk than their younger counterparts for adverse drug reactions and drug-induced illness.(128, 129)

A recent patient care audit at Parkland Memorial Hospital's General Medicine Clinic focused on all elderly hypertensives (65 years of age or older) seen during a randomly picked week (n=102). The ratio of women to men was 4.4 to 1, and the average number of diagnoses per patient was 3.9. The relative frequency of the most commonly associated disease states is depicted in Figure 29. The presence of one or more of these disease states limits the physician's therapeutic options. These patients were receiving an average of 3.6 medications, including an average of 2.1 antihypertensive agents (Figure 30). Tnese findings differ significantly from those previously cited(123, 126) in that psychotropic agents and laxatives were not commonly prescribed by our housestaff and faculty. Goal blood pressure reduction, defined as below 160/90 mmHg, was achieved in 73% of the patients. The failure to achieve satisfactory control was most often due either to patient noncompliance or to the physician's nonaggressive therapeutic approach to hypertension in this age group.(130)

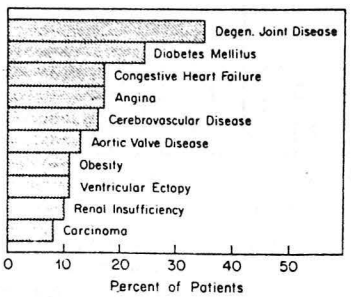


Fig. 29 Frequency of concurrent significant diagnoses in 102 elderly hypertensives.

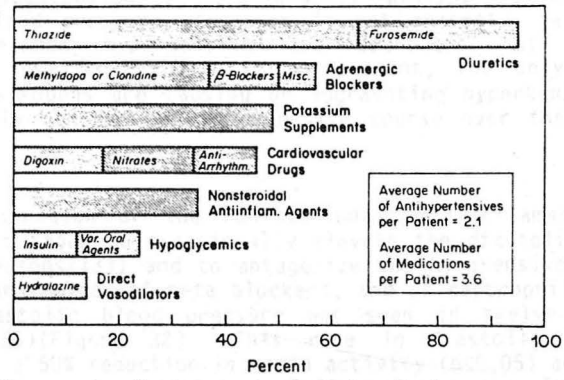


Fig. 30 Concurrent medications commonly employed in the management of elderly hypertensives (N = 102).

Figure 31 illustrates return appointments recorded in the medical chart for 81 of these 102 elderly hypertensives. The interval between visits ranged from less than one month to more than seven months, the average being four months. Considering the complexity of the average patient and regimen, brief yet frequent clinic visits with a nurse practitioner for compliance interventions and drug titration might have proved helpful in achieving therapeutic goals in more of these patients. Occasionally, therapeutic failure or complications of therapy resulted from the use of medications that are either ineffective or poorly tolerated in elderly hypertensives.

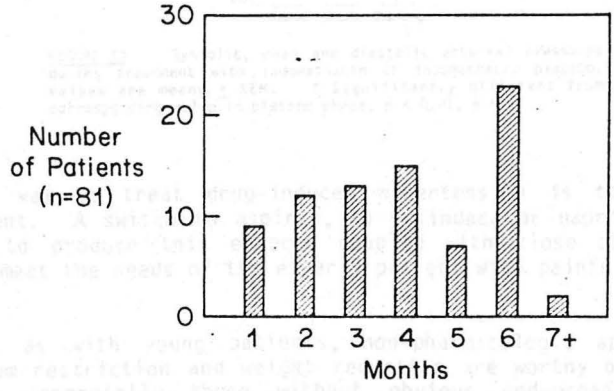


Fig. 31 Number of elderly hypertensives who made return visits at monthly intervals. Of 102 patients, 81 made return visits, the average interval between visits being four months.

Selecting the Proper Treatment Option

The first thing the physician should do before prescribing specific drug therapy for hypertension in the elderly patient is to be sure that a drug-induced blood pressure elevation is not present. A highly significant association between hypertension and estrogens has been reported in post-menopausal females.(131, 132) At present, the only definitive way to ascertain if estrogens are causing or aggravating hypertension is to withdraw them and closely observe the hypertensive course over the next three to six months.

The administration of the non-steriodal anti-inflammatory drug (NSAID), indomethacin, is known to occasionally elevate the diastolic blood pressure in normotensive persons(133) and to antagonize the hypotensive effect of thiazide diuretics or furosemide, of beta blockers, and of captropril.(134) An increase of 9 mmHg diastolic blood pressure was seen in twelve subjects receiving indomethacin.(135)(Figure 32) This rise in diastolic blood pressure was associated with a 50% reduction in renin activity ($p<0.05$) and a 47% decrease in plasma aldosterone concentration ($p<0.05$), however it is the inhibition of prostaglandin synthesis and sodium and water retention that likely causes this phenomenon.

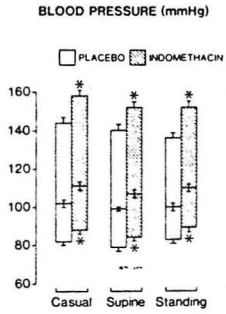


FIGURE 32 Systolic, mean and diastolic arterial pressures during treatment with indomethacin or indomethacin placebo. Values are means ± SEM. * Significantly different from corresponding value in placebo phase, $p < 0.01$, $n = 12$.

The best way to treat drug-induced hypertension is to discontinue the offending agent. A switch to aspirin, to sulindac, or naproxen, NSAID agents less likely to produce this effect, coupled with close observation may be necessary to meet the needs of the elderly patient with painful arthritis.

Secondly, as with young patients, non-pharmacologic approaches such as dietary sodium restriction and weight reduction are worthy of a trial in mild hypertensives, especially those without obvious end-organ damage. These non-drug measures represent lifestyle changes that may be difficult to achieve in the elderly, however, no currently available antihypertensive drug is without its own hazards and these interventions are safe (and cheap).

Thirdly, the evidence of multiple risk factors or evidence of overt end-organ damage should sway one toward the early initiation of drug treatment, but in asymptomatic elderly patients with mild to moderate blood pressure elevations on one casual recording, several more blood pressure recordings to firmly establish the diagnosis is prudent. If the average pressure on three visits exceed a systolic of 160 mmHg or a diastolic of 100 mmHg, treatment can begin, in the meantime non-pharmacological interventions can be ongoing.

Diuretic Therapy

Thiazide diuretics have provided the foundation for antihypertensive therapy in the elderly in a number of long-term studies. Diuretics decrease plasma volume, reduce cardiac output, deplete body stores of sodium, and decrease peripheral resistance over time.(130) The EWPHE Study(36) utilized hydrochlorothiazide plus triamterene and the SHEP(41) study is utilizing low dose chlorthalidone. Each study has achieved significant blood pressure reductions in the majority of their subjects with diuretics alone. The effect of thiazide therapy on isolated systolic hypertension(ISH) has also been studied by Vardan, et al.(136) In 23 ISH patients, older than 50, studied hemodynamically, an elevated systemic vascular resistance (considered as a function of cardiac output) was the most prevalent finding.(Figure 33) The administration of hydrochlorothiazide, 50 mg/day for one month, resulted in a fall in blood pressure in 18 of 20 patients which was characterized by a fall in systemic vascular resistance and stroke volume. After one year of continuous therapy, the hemodynamics, studied in 14 patients, did not change further.(Figure 34)

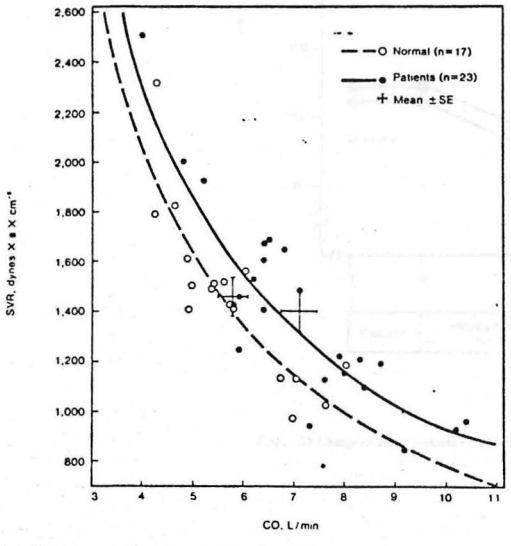


Fig. 33 Broken curved line ($y=-80.28+8,593.16[x]^{-1}$) indicates relationship between cardiac output (CO) and systemic vascular resistance (SVR) in normal population reported by Granath et al[137] (open circles). Solid curved line ($y=-62.27+9,873.93[x]^{-1}$) illustrates relationship observed in our patients with systolic hypertension (solid circles).

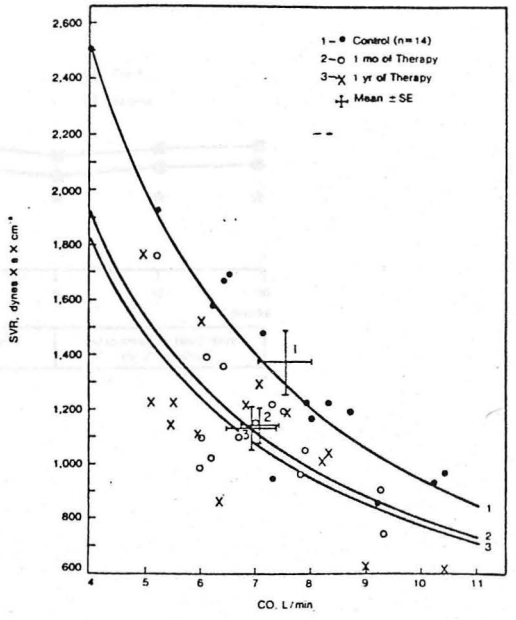


Fig. 34 Relationship between cardiac output (CO) and systemic vascular resistance (SVR) during control state ($y=-134.52+10,686.92[x]^{-1}$), at one month ($y=44.91+7,501.86[x]^{-1}$), and at one year ($y=60.54+7,064.23[x]^{-1}$) of hydrochlorothiazide therapy in 14 patients with systolic hypertension. Curve shifted downward at one month without further significant displacement after one year of therapy.

Indapamide, the prototype of the new class of diuretics, the indolines, has been suggested recently as a diuretic of choice for the elderly. The drug can be given daily or every other day in low doses (2.5 to 5.0 mg), it can be used in patients with mild renal insufficiency and it seems to have an extra-renal effect (probably acting as a calcium channel blocking agent) that potentiates its antihypertensive qualities. Whether this agent is any better than other diuretics remains to be seen, however, a recent study from Belgium by VanHee, et al(137) is encouraging. Twenty-four elderly patients (age 65 to 80) with mild to moderate hypertension were treated in a single-blind trial of indapamide according to the protocol described in Figure 35.

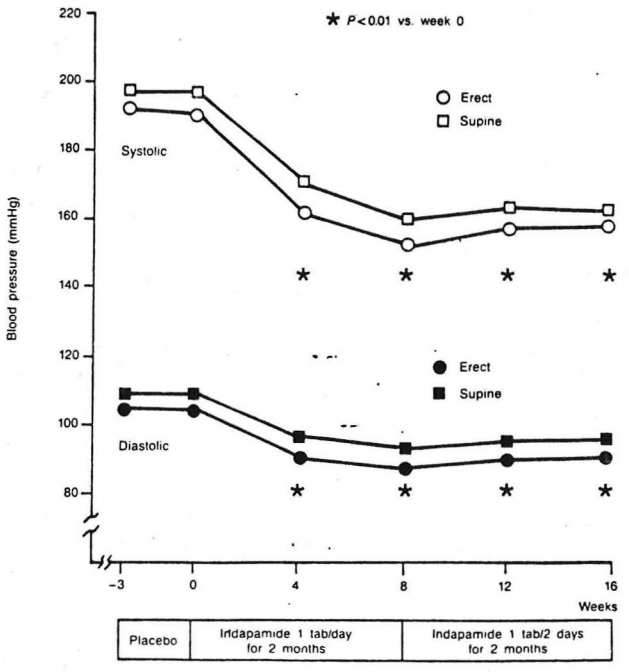


Fig. 35 *Change in blood pressure (18 elderly patients).*

Blood pressure reduction initially achieved on a dose of 2.5 mg. daily for 2 months were subsequently maintained on a 2.5 mg every other day dosage schedule, a schedule that should improve compliance.

Clearly diuretics do lower blood pressure in the elderly, but at what risk? Postural hypotension may result from diuretic therapy in the elderly since they often already have a decreased plasma volume and a blunted baroreceptor mechanism. In elderly patients with glomerular filtration rates below 40 ml/min, furosemide or other loop diuretics may be necessary to effect sodium excretion.(138)

The metabolic consequences of diuretic therapy can be serious in the elderly patient. Severe hyponatremia can be induced by salt restriction coupled with diuretic therapy (particularly with long-acting agents such as chlorthalidone or metolazone).(139) Perhaps the most serious electrolyte disturbance associated with diuretic therpay is hypokalemia. The need to avoid hypokalemia in digitalis-treated patients has been widely accepted, but Holland and associates(140) also demonstrated the development of complex ventricular ectopic activity in hypertensive patients with thiazide-induced hypokalemia. These patients were all under 65 years of age, and none had experienced a previous myocardial infarction or had angina, congestive heart failure, peripheral vascular disease, or complex ventricular ectopy during a normokalemic period prior to starting hydrochlorothiazide, 50 mg twice daily. One would expect diuretic-induced hypokalemia to be even more prevalent in elderly patients, who typically have potassium-deficient diets in addition to underlying heart disease. Potassium supplementation or potassium-sparing diuretics may be necessary in elderly hypertensives, but close monitoring of the serum potassium is necessary because these patients are also prone to hyperkalemia. Moderate salt restriction is useful not only to enhanced blood presure control,(144) but to minimize potassium wastage as well.(145) Thiazide diuretics may cause a deterioration in glucose tolerance(141) and an elevation in serum uric acid, serum cholesterol, and triglycerides.(142) The metabolic consequences of diuretic therapy occasionally become clinically significant in elderly patients.(143)

Except for hypokalemia, the metabolic consequences of indapamide are said to be milder than with thiazide diuretics.(146, 147)

Non-diuretic Therapy

Postganglionic blocking agents:

Reserpine has been chosen in low dose as an alternative at Step 2 (vs. atenolol) after diuretic therapy in the SHEP Study on isolatic systolic hypertension.(41) Reserpine has also been utilized in other major studies in combination with hydrochlorothiazide and/or hydralazine (Veterans Administration Cooperative Study,(17) the HDFP,(29) etc.) and it is effective. Because reserpine depletes neuronal norepinephrine, dopamine and serotonin, serious side effects that mimick illnesses common in the elderly (dementia, depression, Parkinsonism, peptic ulcer, atrioventricular conduction delay) can occur.

Despite the relative low cost and the favorable once per day dosing schedule, reserpine should be avoided in the elderly.(148)

Quanethidine and quanadrel behave as false neurotransmitters entering the sympathetic nerve terminal by the norepinephrine reuptake pump. These drugs block norepinephrine release from peripheral sympathetic neurons upon nerve stimulation and displace norepinephrine from storage vessicles. Initial release of norepinephrine may cause a short pressor response, but it is followed by depletion of catecholamines from nerve terminals of vascular walls and myocardium, resulting in a relaxation of vascular smooth muscle, decreased peripheral resistance, decreased venous return and lower blood pressure.(149) Each of these drugs cause symptoms of orthostatic hypotension and should be avoided in patients with cerebral insufficiency or coronary artery disease. Both drugs interfere with the sympathetic compensatory reflexes of the heart and should be used with precaution in patients with impaired heart function.(150) Both drugs also diminish glomerular filtration rate and renal blood flow and may aggravate azotemia.(150, 151) Sexual impairment may be less of a problem with quanadrel than with quanethidine, but it is still problematic.(152) Quanadrel, with a shorter half-life (12 hours compared to 5 days for quanethidine), tends to be better tolerated, with fewer side effects and a smoother control of blood pressure than quanethidine.(153) Still, neither drug, because of the limitations mentioned, is appropriate for the treatment of elderly hypertensives.

Centrally Acting Alpha-2 Agonists:
(centrally active sympatholoytics)

Methyldopa, clonidine and quanabenz are effective against hypertension in the elderly, combined with a diuretic, or occasionally as monotherapy.(154) These drugs preserve renal and cerebral blood flow and often prove effective in low doses. The fall in arterial pressure from methyldopa is usually associated with a decrease in cardiac output and heart rate in patients over 60 years of age, there is however, no change (or minimal change) in total peripheral resistance as compared to that seen in younger patients.(155) The reflexive cardiac changes that occur in response to isometric exercise and upright tilt remain qualitatively unchanged with this class of drug. Methyldopa may cause significant orthostasis, but this is unusual with low to moderate doses of clonidine or quanabenz. All of these drugs are associated with occasional impotence but at low doses the incidence is also low.

The effects of intravenous clonidine have been studied in patients with congestive heart failure.(156) As expected, intravenous clonidine reduced heart rate and mean arterial pressure, but it also reduced left ventricular filling pressure, mean pulmonary artery pressure, and right atrial pressure as the cardiac output and stroke volume increased. Both systemic and pulmonary vascular resistance fell, as did ventricular preload and afterload. Regional and central hemodynamic variables were ascertained in 10 patients (age range 19 to 67) with congestive heart failure before and after the oral administration of clonidine 0.2 or 0.4 mg.(157) Following the 0.2 mg dose, renal, hepatic and limb blood flow remained unaltered, despite a 10% reduction in heart rate, 14%

reduction in mean blood pressure and a 27% decline in pulmonary capillary wedge pressure.(Figures 36, 37, 38) Cardiac output and peripheral vascular resistance fell slightly, but were not statistically significant. Cardiac output again was unchanged and similar regional hemodynamic changes were elicited except that the peripheral vascular resistance did fall significantly (21%) at the higher 0.4 mg clonidine dose.

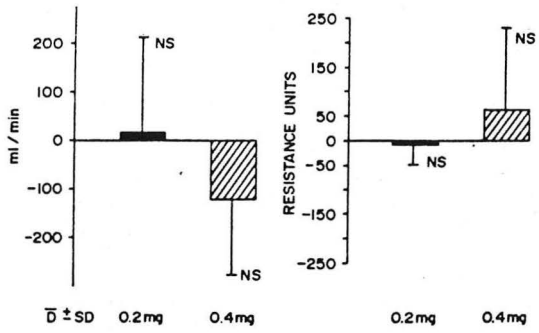
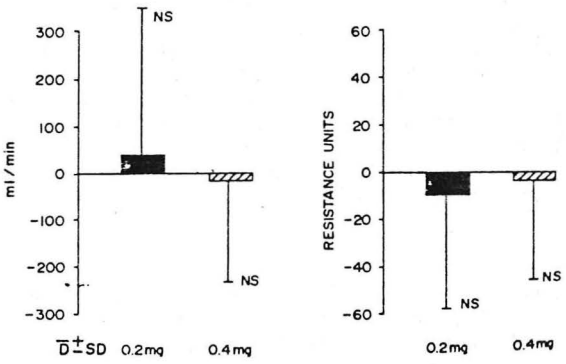


Fig. 36 Clonidine, at both the 0.2 mg and 0.4 mg dose, did not alter renal blood flow or renal vascular resistance. $\bar{D} \pm SD$ = mean of the difference ± standard deviation of the difference.

Fig. 37 Hepatic blood flow **(left)** and hepatic vascular resistance were not changed following 0.2 mg and 0.4 mg clonidine. $\bar{D} \pm SD$ = mean of the difference ± standard deviation of the difference.



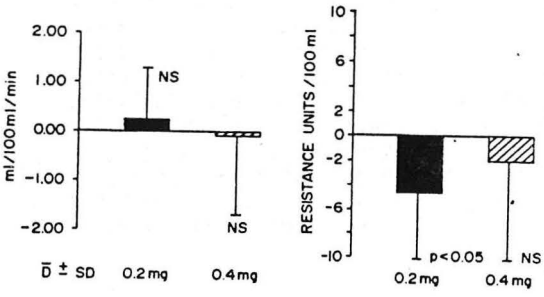


Fig. 38 Limb blood flow was unchanged following 0.2 mg and 0.4 mg clonidine. Limb vascular resistance diminished with the 0.2 mg dose with no significant change following 0.4 mg clonidine. $\bar{D} \pm SD$ = mean of the difference ± standard deviation of the difference.

It would seem that elderly hypertensive patients with congestive heart failure could be treated with clonidine to reduce both preload and afterload without adversely affecting other central and regional hemodynamic variables. Obviously, patients on a long-term oral regimen will have to be studied before stronger recommendations can be made.

Tne metabolism of methyldopa and quanabenz is primarily hepatic and one of the chief concerns with methyldopa is drug-induced hepatitis.(158) Liver function tests should be monitored closely during the first two months of therapy and thereafter every six months. After oral administration, 40 to 50% of clonidine is excreted unchanged by the kidney in 24 hours.(159) The mild renal insufficiency common in many elderly patients may allow small doses of clonidine to be effective on a once per day dosing schedule. Even in patients with normal renal function, we previously demonstrated that the twice daily dose of clonidine, with a single daily dose of chlorthalidone, could be given all at bedtime without compromising blood pressure control.(160) Similar findings were reported by Noveck and associates(161). Because methyldopa, clonidine and quanabenz all cause sedation, particularly at the onset (first three weeks) of therapy, small doses of these agents should be titrated into the regimen at bedtime. In the elderly, low dose is preferred to start (125 to 250 mg methyldopa, 0.1 to 0.2 mg clonidine, 4.0 mg of quanabenz). Clonidine and quanabenz have an onset of action within one hour of oral administration so that the effect of small doses can easily be evaluated in elderly patients. It is our practice in the elderly to titrate slowly at the bedtime dose every week or two weeks until a dose of 0.3 mg clonidine, or 500 mg methyldopa is reached before going to a morning dose. Twice daily doses of quanabenz are usually required from the beginning. The side effect of sedation occurs with all of these drugs. With clonidine perhaps this can be turned into a therapeutic plus. Many elderly patients complain of sleep disturbances and request nighttime hypnotics. Clonidine 0.3 mg has been shown to provide a similar duration and pattern of sleep as that achieved with the benzodiazepine, nitrazepam (20 mg), in normotensive subjects,(162) so that it might be useful in hypertensive patients with sleep disturbances.

Unlike methyldopa, there are no contraindications to clonidine or quanabenz therapy, but all of these agents do have an associated abrupt discontinuation syndrome, particularly at higher doses or when combined with non-selective beta-blocker therapy.(163) A new delivery system is currently being evaluated for clonidine which is similar to the transdermal systems for scopalamine, digoxin and nitroglycerin except that it yeilds therapeutic levels (after reaching a steady state at 48-72 hours) for one week or more.(164, 165) Two-thirds of 85 patients with mild hypertension, receiving one to three 0.1 mg/day patches, had an excellent response and achieved diastolic blood pressures below 90 mmHg with this delivery system.(164) Drowsiness was reported to be milder with this delivery system than with oral adminstration. Some mild pruritis and localized erythema occurred, but 6% of the patients had significant skin reactions requiring discontinuation. If this delivery system is affordable for the elderly, it may hold promise for improving compliance while altering lifestyle only minimally.

Beta Blocking Agents:

Beta-blocking drugs, at first glance, would appear to have the advantage of lowering supine or standing blood pressure without causing orthostasis. A second look, however, raises questions concerning the logic of this choice for elderly hypertensives. Beta-blockers reduce cardiac output and increase peripheral vascular resistance, thereby intensifying the physiological changes associated with aging and chronic hypertension. In patients with borderline cardiac compensation, beta-blockers may precipitate congestive heart failure, primarily by blocking the compensatory increase in heart rate associated with this state. The likelihood of this complication is greatest during the early titration process as the heart rate is reduced.(166) Close followup is mandatory, and we recommend serial chest x-rays to compare cardiac-thoracic ratios before and after treatment. A careful history exploring for symptoms of dyspnea on exertion, shortness of breath at rest, orthopnea, and paroxysmal nocturnal dyspnea should be obtained prior to initiating beta-blocker therapy. Beta-blockers can cause sinus bradycardia and AV conduction delay or block; in fact, heart block greater than 1° AV is a contraindication to therapy. Beta-blockers do decrease the reflex autonomic activity associated with direct vasodilator therapy, which can be helpful in patients with angina. Beta-blockers can be used in the management of hypertension in the elderly, but are best reserved for patients who also suffer from angina,(167) have had a recent myocardial infarction,(168) or have an arrhythmia sensitive to beta-blockade.

Several recent reviews recommend beta-blockers as either first- or second-step therapy in elderly hypertensives.(169, 170) This is somewhat ironic because beta-blockers are often less effective in this age group, either because of a change in beta-receptor number or sensitivity or because these patients generally have lower renin levels. Buhler and co-workers(171) demonstrated that therapy with propranolol alone was successful in 90% of hypertensive patients in their 20's, whereas only 20% of 60-year old hypertensives responded as well. Other studies focusing on the elderly used a beta-blocker alone(172) or in combination with a diuretic(173, 174) and reported favorable reduction in blood pressure. If possible, however, beta-blockers should be avoided in patients with reversible airway disease, brittle insulin-dependent diabetes, or a history of anaphylaxis or allergic rhinitis. Elderly hypertensive patients may also suffer from peripheral vascular disease. Compared to the centrally active sympatholytics, non-selective beta-blockers have a higher incidence of cold extremities(175) and they are known to reduce resting forearm blood flow by peripheral vasoconstriction(176) a situation that could result in an exacerbation of intermittant claudication. While this is occasionally seen clinically, several controlled studies suggest that as obliterative arterial changes become more extensive, beta blockade, irrespective of its type, loses its hemodynamic effect or peripheral circulation.(177) The few controlled studies available on walking capacity in patients with intermittant claudication fail to demonstrate an exacerbation during long-term beta-blocker therapy.(178, 179) When beta-blocker therapy is unavoidable because of associated disease states such as ischemic heart disease, cardioselective (B_1) blockers, such as metoprolol or atenolol, should be used. Patients with concomitant ischemic heart disease are at greatest risk for the withdrawal syndrome associated with sudden discontinuation of beta-blocker therapy. The syndrome may be mild (nervousness, tachycardia, headaches, nausea, etc.), or it may be unpredictably severe (exacerbation of angina, myocardial infarctions, ventricular arrhythmia, even sudden death).(163, 180) All beta-blockers should be withdrawn slowly over two to three weeks.

Important drug interactions with beta-blockers in elderly hypetensives include a reduction in insulin release with oral hypoglycemic therapy (less for patients receiving cardioselective blockers),(181) hypertension and bradycardia during insulin-induced hypoglycemia (less for patients receiving cardioselective blockers),(182) masked catecholamine-mediated symptoms during insulin-induced hypoglycemia (with any beta-blocker), and a reduction in blood pressure control in patients receiving a beta-blocker and an alpha-vasoconstrictor (over-the-counter decongestants, epinephrine, clonidine).(183) The antihypertensive effect of propranolol is attenuated by indomethacin, which suggests that the antihypertensive effect of beta-blockade may be mediated in part by prostaglandins.(184) Blood pressure should be closely monitored in elderly patients receiving beta-blocker therapy if a nonsteroidal anti-inflammatory agent is added. Although significant CNS disturbances (nightmares, confusion, hallucinations, depression, etc.) can occur in the elderly receiving beta-blocker therapy, these symptoms can be largely avoided by using agents that are highly soluble in water but not in lipids. Nadolol and atenolol do not cross the blood-brain barrier to any great extent.

Labetalol, a drug with beta and alpha blocking properties (3:1 ratio), has been effective in treating mild to moderate hypertensive elderly patients (N=27, mean age 66) with predominantly low doses (100 mg BID) in a study by Eisalo and Virta from Finland.(185) Higher doses tended to cause orthostasis and malaise which could limit the drug's usefulness.

The final precaution regarding use of beta-blockers in the elderly concerns the effect of aging on the pharmacokientics of these agents. The water-soluble drugs are primarily excreted unchanged by the kidney; their half-life allows for single daily doses. Because of the decreased renal function in the elderly, low doses of these drugs must be used to avoid accumulation and potential toxicity. On the other hand, the distribution of propranolol to tissues appears to be slowed in elderly hypertensives.(186) An increased bioavailability following oral administration (diminished intrinsic clearance or first-pass kinetics) has been demonstrated for propranolol(186) and metoprolol in the elderly. Perhaps these drugs can be given in lower doses, or even once a day in the case of metoprolol, to avoid toxicity.

Vasodilators:

Vasodilators, on theoretical grounds would seem ideal for elderly patients, however, side effects and compensatory responses limit their usefulness.

Prazosin, a selective alpha-1-antagonist,(187) should be used with caution in the elderly because of orthostasis. First-dose syncope is an overstated problem, which can be generally avoided by giving an initial dose of 1 mg at bedtime and then titrating the dose slowly upward, from 1 mg thrice daily to a twice daily regimen of up to 20 mg/day. The dose should be titrated no more frequently than weekly or biweekly in the elderly. This drug has been used

Recently, the effects of nifedipine monotherapy with retard (slow release) tablets, 20 mg twice daily were evaluated in 23 elderly hypertensive patients (mean age 79).(195) Patients with advanced renal insufficiency, severe heart failure or a recent cerebrovascular event were excluded. Average blood pressure was 191 ± 2.4/96 ± 1.8 mmHg in the total group. A subgroup of five patients with ISH, had a blood pressure of 184 ± 4/79 ± 3 mmHg. After a 20 mg nifedipine tablet was given, a maximal effect was seen at 2 hours when blood pressure fell from 188.5 ± 6.2/97.5 ± 3.4 to 143 ± 4.9/76 ± 4.9 mmHg.(Figure 39) A non-significant heart rate was noted and no side effects occurred. The fall in blood pressure in the ISH subgroup was greater for systolic than for the diastolic.(Figure 40) Twenty-one of 23 patients completed the study (2 dropped out because of side effects) and at the end of 8 weeks, 15 patients (71%) reached the goal of a blood pressure of ≤ 160/90 mmHg and 4 (19%) others had a decrease in diastolic blood pressure between 15-28%.(Figure 41) At 8 weeks, the standing heart rate was slightly higher than the sitting (p=0.02) but orthostasis was not a problem. Pedal edema (26%), facial flushing (22%), weakness (13%), headache (13%), and dizziness, fine tremor, and nocturia (each 4%) were experienced, but only in the case of one patient with headache and one patient with severe pedal edema were the side effects significant enough to discontinue treatment.

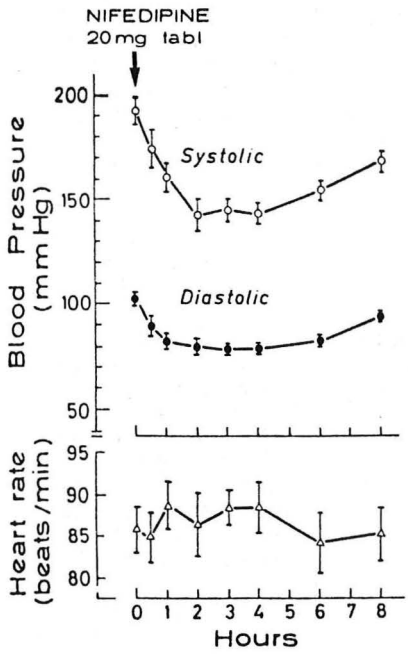


Figure 39

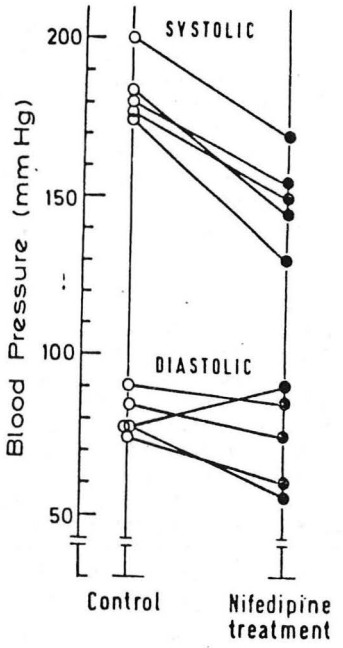


Figure 40

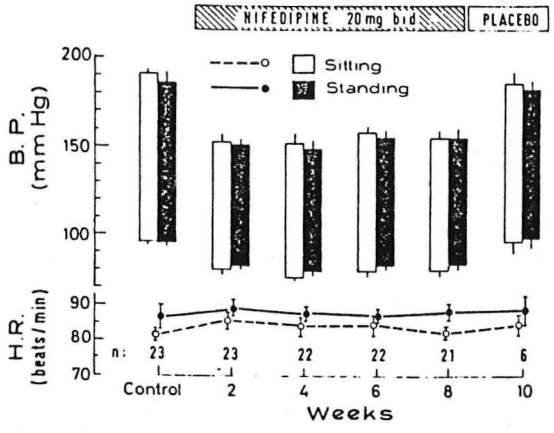


Figure 41

Converting Enzyme Inhibitors:

The antihypertensive efficacy and tolerability of captopril has been documented in mild and moderate hypertension(196) and in severe hypertension(197, 198) associated with high renin activity. In high renin states, captopril inhibits the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and stimulant of aldosterone production, resulting in a corresponding reduction in total peripheral resistance and blood pressure.(199) Captopril has also been shown by Holland, et al(200) to lower blood pressure in black patients with low renin, essential hypertension. Captopril's precise mechanism in low or normal renin patients is not fully known but in part relates to the block of bradykinin (a potent vasodilator) degradation.(201) Captopril also increases the levels of plasma and urinary metabolites of prostacyclin(201, 202) and its antihypertensive effect is inpaired by indomethacin.(203)

In the elderly hypertensive, monotherapy with captopril was recently compared to diuretic therapy with chlorthalidone. Twenty hypertensive patients over age 65 (mean age 70.1 years) were randomized to captopril 50 mg twice daily or chlorthalidone 25 mg daily for a three-month period. The results are summarized in Table 16. Both treatments were equally successful and equally well tolerated, however, captopril induced fewer biochemical changes, particularly in terms of blood glucose and serum potassium. The vasodilatory response to captopril in also quite useful when carefully applied to the patient with congestive heart failure.(206) Not only does the agent provide a reduction in afterload and preload, it also decreases secondary aldosteronism and promotes a diuresis in patients that are "refractory" to low dose thiazide diuretics. This same benefit from low-dose captopril is available in low-renin hypertensive patients.

Table 16 *Effects of captopril and chlorthalidone on blood pressure, heart rate and biochemical parameters*

Parameter	Captopril		Chlorthalidone	
	basal	3rd month	basal	3rd month
Systolic blood pressure (mmHg)	170.0 (11)	152.4 (7)	171.0 (8)	151.5 (6)
Diastolic blood pressure (mmHg)	98.5 (3)	86.0 (3)	99.0 (3)	87.0 (6)
Heart rate (bpm)	76.0 (4)	75.6 (6)	78.0 (5)	80.4 (5)
Serum creatinine (mg/100 ml)	0.91 (0.06)	0.90 (0.07)	0.90 (0.08)	0.9 (0.06)
Serum glucose (mg/100 ml)	87.8 (7)	87.9 (5)	89.9 (9)	95.4 (7)
Serum triglicerides (mg/100 ml)	136 8 (33)	127.1 (32)	136.7 (29)	142.5 (31)
Serum sodium (mEq/l)	135.6 (4)	135.8 (3)	137.5 (5)	135.5 (5)
Serum potassium (mEq/l)	4.2 (0.3)	4.4 (0.4)	4.2 (0 3)	3.7 (0.3)

Data expressed as mean (SD).

CONCLUSION

The treatment of hypertension in the elderly is clearly warranted and it may provide one of the most effective preventive interventions available in this population. The emphasis of antihypertensive therapy (as with regimens directed at other chronic problems in the elderly) should be to increase or maintain functional status as much as to extend survival.

The elderly hypertensive has special needs that may be more important than therapeutic goals physicians tend to set for their patients. The patient's special needs, concerns and fears must be recognized. The therapeutic regimen must be simplified, ritualized, and made a part of daily living; it must be affordable and it should not result in excessive morbidity. To achieve these goals, the physician must understand the physiological process of aging, the pathophysiology of hypertension in the elderly, and the outcome desires of the patient. The physician must also know how to access and use both the formal and informal support systems that surround the patient.

The practice of preventive medicine in the elderly can be caring and cost-effective, thereby meeting the needs of society by meeting the needs of the individual patient. That is the opportunity and the challenge.

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Understanding Adherence Behavior in the Elderly

Ron J. Anderson, M.D.
President & Chief Executive Officer
Parkland Memorial Hospital
Associate Professor, Internal Medicine
The University of Texas Health Science
Center at Dallas

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Parkland Medical Grand Rounds
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Part III: Understanding Adherence Behavior in the Elderly

UNDERSTANDING ADHERENCE BEHAVIOR IN THE ELDERLY

Introduction

Patient noncompliance with prescribed medications and dietary instructions is the most important reason for failure to achieve goal blood pressure reduction in the office management of hypertension.(1) Certain features of the aging process and changes in social support systems increase the likelihood of noncompliance in elderly hypertensives. The optimum management of any chronic disorder requires a mutual understanding and acceptance of the physician's and the patient's roles and responsibilities.(2) The physician must assess the patient's knowledge, coping skills, attitudes, and health beliefs to help the patient help himself.(3) He or she must also provide an accurate diagnosis and an individualized therapeutic plan. The physician's roles, therefore, are diagnostician, guide, and patient advocate. Nonetheless, it is the patient who ultimately decides whether to follow instructions or to report regimen problems to the physician. The roles of the patient, therefore, are decision-maker, problem-solver, and self-advocate. A therapeutic partnership can be encouraged by mutual participation in goal-setting and by eliciting informal informed consent (verbal contracts).

A physician should not presume to understand the relative value an elderly patient might place on otherwise "obvious" therapeutic goals of blood pressure reduction. Surviving in a compromised or dependent period of compressed morbidity, or worse yet, a "pre-death" state(4), is not a therapeutic goal for many elderly patients, it is instead a worst fear realized. In trying to enlist a patient's commitment to a therapeutic plan, which in the best of circumstances complicates the patient's life with new costs, life-style change and perhaps drug side effects, emphasis should be placed on the avoidance of morbid events (congestive heart failure, cerebrovascular accident, renal insufficiency, etc.) and the maintenance of independence and functional capacity if extension of life is not the patient's primary concern.

The essential step of discussing a patient's desired outcomes is too often overlooked in place of establishing unilateral therapeutic goals defined in statistical and epidemiologic terms.

Physician Attitudes that Compromise Care in the Elderly

Physicians are accustomed to gathering historical data and weighing physical findings and laboratory results in the development of a disease-oriented differential diagnosis. The evaluation of elderly patients need not include a detailed history of genetic disorders or risk factors identified with premature cardiovascular disease, whereas a careful psychosocial assessment and an inventory of formal and informal social supports, financial capability and functional status is fundamental. The utilization of diagnostic interventions should be weighed in terms of maintainance or improvement of functional status and then balanced against the consequences of possible iatrogenic risks (the "principle of minimal interference"(5).

Sometimes the dignified care of the elderly requires a physician to do a self-survey of attitudes concerning the elderly.(6) Elderly patients may stimulate anxiety or fear in the caregiver who has not yet dealt with personal feelings concerning aging and death. A heavy orientation toward curative medicine may cause a physician to subliminally minimize the importance of preventive interventions in the elderly because of the obvious limitations in extending expected survival. Over emphasis on "cure" may compromise care. The death of any patient, no matter the age or underlying illness, may challenge the self-worth and sense of effectiveness of some physicians. Occasionally, an elderly patient represents a parental figure to a physician with unresolved parent-child conflicts and thereby arouses uncomfortable feelings or anxieties in both parties. Solomon and coworkers(7) studied the effect of age on the duration of medical encounters with physicians. The encounter time was either the same or less for patients aged 65 or over as for those aged 45 through 64, regardless of the severity and complexity of the illness. The investigators had assumed that physicians would spend more time with the elderly, who might have more complex medical problems, requiring more of the physican's attention. The findings suggest that many physicians decided (whether consciously or not) to allot less time to elderly patients, perhaps revealing their attitudes toward the elderly.

Physicians would not tolerate 50% error rates or failures in diagnostic tests or alternative therapies, but they often accept the same end-product by failing to understand, recognize and modify factors that either impede or enhance compliance in the elderly.(8) Multiple factors are at work in each physician-patient relationship and the delivery setting, severity of illness, and regimen also affect compliance behavior. In the following tables, factors strongly supported by available literature are termed "hard" conclusions, those that are only suggestive are termed "soft" conclusions.

Human Factors Influencing Compliance (Table 1)

Patient Factors

It is difficult to separate certain patient factors from obvious structural barriers that impede cmpliance in some populations. Becker's(9) review of compliance studies suggests that black blue-collar workers with low educational levels comply least well. Language and ethnic barriers may play a significant role in noncompliance. Similarly, structural barriers can be identified for elderly hypertensives. Such patients often live on a fixed income at or near poverty level; they may have limited transportation resources and may have to depend on others as access to health care, and they may fear being victimized en route to see the physician.(10) Masked depression or grieving after the loss of a spouse may result in self-neglect and noncompliance. The death rate of elderly widowed men for several years after the spouse's demise is consistently higher than that of widowed women.(11) Remote or recent memory or both are often impaired in the elderly(12), and early stages of dementia may not be obvious from cursory evaluation. Hearing impairment is a common cause of miscommunication leading to non-compliance or medication error.

The elderly are not immune from personality traits that impede compliance. Hypochondriasis, paranoia, the type A personality,(2) and deep-seated hostility and aggression toward authority figures(13, 14) tend to decrease compliance in all age groups.

Table 1 Human factors influencing compliance.

	Hard Conclusions	Soft Conclusions	No Consistent Association
Patient factors	+Patient perception of vulnerability to disease	+Family expectation favoring compliance	•Religion
	+Presence of coping and communication skills	±Patient education and actual knowledge about disease	
	−Social isolation	+Internal versus external locus of control	
	−Presence of psychiatric or personality disorders	−Extremes of age	
		−Low income	
		−Lower educational level	
		−Ethnic or language barrier	
		−Single or widowed	
		±Female	
Physician or health-care provider factors	+Positive attitude (enthusiasm)	−Dissatisfaction with provider	•Clinician's prediction of compliance
	+Length of physician-patient relationship	±Clinical setting (surroundings and plant)	•Clinician's knowledge of the actual seriousness of the disease
	+Time spent with the patient		
	+Specificity and clarity of communications		
	+Provision of positive feedback		
	+Accommodation to patient's beliefs and personality		
	+Patient satisfaction at the end of an encounter		
	−Long waiting periods		
	−Extended period between hypertensive screening and appointment		

+ = Positive association.
− = Negative association.
• = No consistent association

The attitude of an elderly patient toward himself and the illness often predicts behavior. Compliance should result if the appropriate knowledge, skills, and resources are available and if the patient peceives the illness as a threat to well-being, recognizes the value of reducing the threat, and his ability to do so by following instructions ("health belief model").(15) What a patient perceives (or feels) is probably more important than what he truly knows. The potential for a desired behavior to occur in a given psychological situation is a function of the expectancy of a particular valued reinforcement. Locus of control social learning theory may be relevant to the study of compliance in elderly hypertensives.(16) In this concept, persons with an internal locus of control note contingencies between their actions and subsequent events, and, given a proper health belief, tend to seek out more information about their illness and health maintenance.(17) In general, "internals" are likely to keep appointments and take medications once they understand the benefits of therapy. A negotiated approach to management of the illness is particularly useful in dealing with these patients. "Externals" tend to assume that events are preordained or a function of fate, luck, or powers beyond personal control. Since many elderly patient depend on external resources, hence external controls, interventions designed to encourage internality may have only a modest impact. Nonetheless, as far as is possible, educational and motivational interventions should be used to maximize functional status by strengthening coping skills, by convincing the elder of the gains of therapy and by encouraging proper use of health-care resources. Independence should be fostered during the negotiation of therapeutic goals and treatment plans by offering options when possible. The physician and the family should use positive feedback to reinforce desired behavior and to enhance the elderly person's self-esteem and worth.

While some elderly patients under-utilize physicians because they attribute certain symptoms to "just getting old", others may contact physicians for routine checkups in the absence of symptoms and "overuse" health care resources for nonserious and multiple complaints.(18) The elderly patient with a non-descript illness or well-described multiple complaints, may be suffering from masked depression or a need for socialization. In either case, the physician needs to bring this important human need to the attention of "significant others" in the family. When necessary the physician can serve as a catalyst to help harness available community resources to meet this need. If the patient is ambulatory and the family or others are willing to provide transportation, outings can be prescribed or the use of day care and nutrition centers can be suggested. Getting the elderly patient to become involved outside the home in church or civic activities or as a senior volunteer tends to focus their attention on others and away from their own disabilities and discomforts.

Physician Factors

Physicians seem to have difficulty recognizing noncompliant patients at the time of an office visit.(19-21) An educational program aimed at increasing physician awareness of the problems of noncompliance with antihypertensive medication resulted in a nearly twofold increase in the number of patients taking at least 75% of their medications and achieving blood pressure control.(22)

Certain attributes of the health care provider are particularly important, for they improve the patient's feelings about the physician and result in improved compliance. Continuity, comprehensiveness, accessibility,(23) empathy and concern,(24) specificity and clarity of communication, and enthusiasm(25) are highly valued physician characteristics. Enhancing patient satisfaction may be pivotal to the care of patients with chronic illness. Bartlett, et al(26) found that the quality of interpersonal skills influenced patient outcomes more than quantity (and quality) of teaching and instruction. A secondary analysis of their data reveals that all the effects of physician communication skills on patient compliance were mediated by patient satisfaction and recall. A stable relationship between the health care provider and patient and decreased waiting periods were the primary reasons cited by patients for improved appointment keeping and medication taking in an inner city black population.(27) Reorganizing a hypertension clinic to provide continuity of care, easy access, and shorter waiting periods increased the rate of appointment keeping from 50% to 84%, and blood pressure control was achieved in 70% of patients compared with 10% and 17% in control populations. Health care providers must be willing to change the structural and functional components of a clinic system to meet patient's needs and maximize compliance. Physicians may also have to alter their practice style with elderly patients. A more concentrated communications effort is necessary to explain in clear and explicit terms the nature of the disorder and the necessity of treatment. Allowances for the sensory impaired must be made, sometimes with a written explanation. Female physicians may have to lower their voices for their hearing impaired patients. Whether verbal or written, the instructions should also be reviewed when possible with a patient designated member of the family or informal support system.

Illness Factors Influencing Compliance

Illness factors that influence compliance are summarized in Table 2. Luntz and Austin(28) found that only 30% of patients on antituberculosis medication continued therapy for a recommended four years. In general, compliance diminisnes in direct relation to the duration of recommended therapy. In a disease with symptoms that are unpleasant to the patient, therapy that alleviates the symptoms encourages compliance. If noncompliance results in a rapid return of recognizable symptoms, the patients are more likely to reinstitute therapy. Many patients become fatigued or willing to take a chance after initially good participation because symptoms have become remote memories. Symptom reinforcement can be replaced by physician or family reinforcement through positive feedback and encouragement. Hypertension is a lifelong malady that is usually asymptomatic both before diagnosis and during periods of noncomplicance. If hypertension is not perceived as an illness, the health care provider's job is more difficult and requires considerably more attention to patient education and motivation. The advantages of consistent goal blood pressure control have to be made clear to the patient and reinforced frequently.

Table 2. Illness factors influencing compliance.

Hard Conclusions	Soft Conclusions	No Consistent Association
+ Previous bout of same illness	+ Extent that therapy relieves symptoms	• Actual seriousness of the illness
+ Similar illness in family or friends	+ Extent that noncompliance causes recognizable symptoms to reappear	
− Chronic illness	− Excessive anxiety or fear	
− Asymptomatic illness		

+ = Positive association.
− = Negative association.
• = No consistent association.

When compliant patients with severe hypertension were asked why they had adhered to physician recommendations, 50% reported that a friend of family member had suffered illness or death related to high blood pressure.(29) Perhaps these patients perceived that they, too, were vulnerable to this disease. Nonetheless, physicians should avoid generating excessive fear of the stress hypertension imposes on certain organ systems and the threat of life itself. Neurotic anxiety often interferes with compliance(30), as does denial or feelings of invulnerability. One of the best predictors of good compliance is the patient's behavior during past or concurrent illnesses.(31) Most elderly hypertensive patients have several concurrent illnesses, which increases the complexity of therapy and the likelihood of drug interactions and decreases compliance. Limited financial resources may cause such patients to set priorities that focus on symptom relief (of arthritis, constipation, chronic anxiety) rather than on preventive care. A mean number of 3.9 diagnoses per hypertensive patient age 65 or older was derived from a chart audit at Parkland Memorial Hospital's General Medicine Clinic and represents all such patients (N=102) seen during a randomly selected week.(32)(Figure 1)

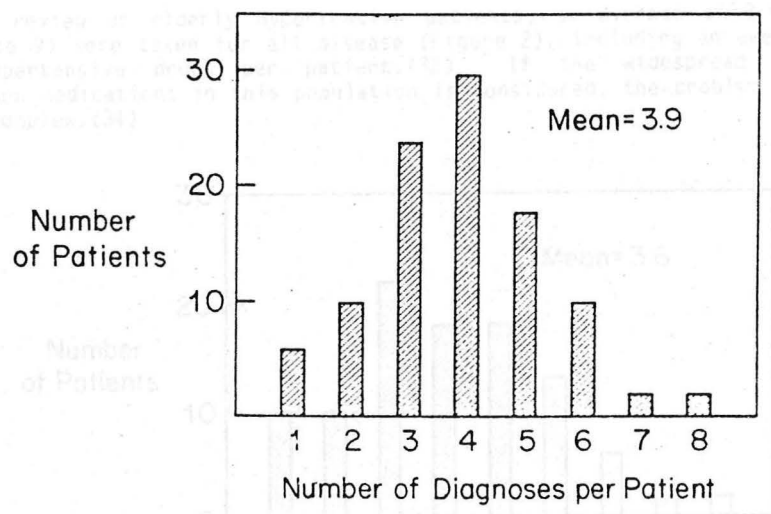

Figure 1. Number of diagnoses per patient shown in charts of 102 hypertensive patients aged 65 or older.

Regimen Factors Influencing Compliance

Regimen factors that influence compliance are summarized in Table 3. A consistent increase in drug use by therapeutic category occurs with increasing age. Hale and associates(33) found that 76.6% of 1,711 elderly patients undergoing hypertensive screening were regularly using a drug preparation. In fact, the average number of drug categories used was 1.6 for patients 70 years old compared with 2.6 for patients 84 years or older. The most commonly used drugs were antihypertensives, cardiovascular agents, vitamins, and internal analgesics.

Table 3. Regimen factors influencing compliance.

Hard Conclusions	Soft Conclusions
−Complexity	+Patient perception of efficacy
−Frequency of administration	+Extent that therapy relieves symptoms
−Prolonged duration of therapy	±Type of medication (tablet, capsule, liquid, etc.)
−Other behavioral changes demanded	−Number of pills per dose
−Costs of therapy	−Side effects

+ = Positive association.
− = Negative association.

In our review of elderly hypertensive patients, an average of 3.6 drugs (range, 1 to 9) were taken for all disease (Figure 2), including an average of 2.1 antihypertensive drugs per patient.(32) If the widespread use of nonprescribed medications in this population is considered, the problem becomes even more complex.(34)

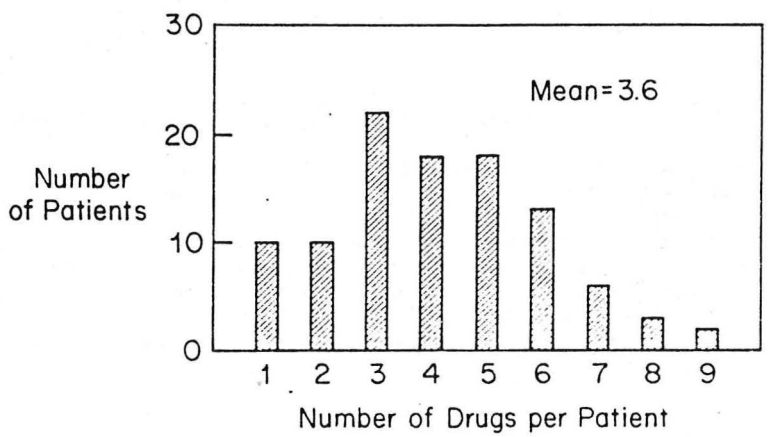

Figure 2. Average number of drugs taken for all illnesses by 102 hypertensive patients aged 65 or older.

Multiple medications and complicated schedules can be confusing and often lead to medication error or noncompliance in elderly patients. The best rule is simplicity. Drug regimens should be as ritualized as possible. Twice daily or single bedtime doses should be the rule, and fortunately, most antihypertensive agents can be given less frequently in the elderly. The number of medications per dose seems less important than the frequency of dose in determining compliance.(35) Complicated regimens can be simplified by the use of compartmentalized containers set up by a family member or nurse. Products should be labeled (drug name and use), and medications should be brought in for review on each clinic visit. Easily identifiable products (color or shape) make it easier for the physician to discuss medication problems with patients who call when their charts are not available.

Once a regimen has been individualized, a physician may choose to use a fixed dose combination product to simplify the regimen. These agents are acceptable when used by physicians knowledgeable about their components. They are often more convenient and offer the advantage of decreasing the total number of prescriptions, a benefit particularly for elderly patients who depend on government programs for some of their prescription needs. Some of these formulations are cheaper than their components. The physician must become aware of the cost of medications as well as the cost to the patient for transportation and follow-up visits. The patient's feelings about these costs should be explored in an effort to make realistic decisions regarding drug therapy. For example, can dietary manipulation or a salt substitute (a few pennies a day) meet the needs of a patient taking a diuretic without a prescription for potassium supplements, or can the use of natural laxative cereals and an intake of adequate water avoid medicinal laxatives.

Side effects are commonly blamed by physicians for noncompliance with antihypertensive therapy; however, most patients who drop out of treatment actually feel well.(29) In a therapeutic partnership, side effects may be a cause for renegotiation of the medical regimen, but not for noncompliance. Side effects from medications are more likely in the elderly for a variety of reasons. The side effects of some drugs can often be minimized with appropriate dosage schedules, which may also improve compliance (for example, clonidine at bedtime).(36) Medical recommendations that change a patient's lifestyle (for example, salt restriction, weight loss, discontinuance of smoking) tend to influence compliance behavior more negatively than merely prescribing oral medication. It is wise to approach only one bad habit at a time and not until compliance with medication has been maximized.

Improving Patient Compliance in the Ambulatory Setting

The first step toward improving compliance is the recognition of a physician's frequent inability to predict adherence to a treatment regimen. For example, residents at Johns Hopkins did little better than chance in predicting patient compliance.(37) Several methods are beneficial in assessing patient compliance during an office visit. The ultimate test, a surprise home visit to measure blood pressure or to check for serum or urinary drug markers, however, often yields discrepant results.(38) Physicians should interview patients in a supportive way, avoiding blame and conversely, avoiding forcing the patient "to

please the doctor" with a less than correct response. A patient's admission of noncompliance in a nonthreatening interview is highly predictive, whereas a denial of noncompliance means little. During interim interviews, it is helpful to go through a checklist of items that affect compliance and ask about side effects, costs, or difficulties with remembering to take medications on schedule. This approach is valuable in patients that are meeting their goals and are presumed to be compliant since it reinforces the importance of compliance and the ground rules of a therapeutic partnership. It also expresses the physician's concern, empathy, and interest in the problems the patient may have in adjusting to his illness.

Pill counts or review of prescription refills done in an unobtrusive manner may be useful indicators of compliance, but obvious deceit can still occur. Pharmacological effects (for example, bradycardia, orthostasis, blood pressure control) or metabolic consequences of therapy (for example, hyperuricemia or hypokalemia with thiazide diuretics) indicate some degree of compliance even though they are not desirable. The report of commonly associated side effects may mean that the patient is complying, but it may also mean that a change in dosage schedule or drug choice is needed. We have found home visits by office personnel or visiting nurses to be particularly useful in confirming noncompliance and in assisting in problem-solving. This approach also decreases transportation problems for elderly patients.

Education alone may be an insufficient guarantee of compliant behavior in hypertensive patients, young or old.(39) As a minimum, however, certain facts should be transmitted to all patients. They should know that hypertension is a disease that often is asymptomatic. If left untreated, the disease may cause brain, heart, and kidney damage or untimely death. The disease is a lifelong malady that requires continuing physician supervision and treatment, but control can be achieved by participation in a mutually designed treatment plan. Educational material should not be too threatening but should instead focus on therapeutic gains.

Recently, Morisky, et al(40) at Johns Hopkins School of Hygiene and Public Health studied the effects of a health education program on compliance in over age 65 hypertensives (N=90) compared to younger patients (N=260). Despite the fact that elderly patients had more chronic disease, more complications from hypertension, and were receiving more complex drug therapies than younger patients exposed to the same interventions, they demonstrated significantly higher levels of compliance with appointment keeping and drug taking. The education program consisted of a 5 to 10 minute counseling interview immediately following the medical encounter. This session was intended to clarify and emphasize the importance of the therapeutic regimen to foster family understanding, support and reinforcement for the patient. A series of three one-hour group sessions followed which focused on increased patient understanding and feelings of self confidence. This study stressed the fact that educational and motivational programs can be successfully directed toward the elderly.

Recently, the Hypertension Clinic of Tucson Veterans Administration Medical Center studied the effect of 1) advice; (Group A) 2) an intensive educational program; (Group B) and 3) small group management plus feedback on 48 outpatients, aged 40 to 69 years (Group C).(41) During group sessions held for one hour each week for eight weeks, the leader of Group C discussed sodium

content of certain foods, medication compliance, perceptions of severity of illness, personal suspectibility, belief in treatment effectiveness, and satisfaction with treatment. Feedback consisted of sharing information on blood pressure levels and urinary sodium content before the first, after the second, fourth, sixth, eighth week, and monthly thereafter. In the one year study, group management plus feedback to patients was more effective than advice or intensive educational effort, but overall compliance was still poor in all three groups (54%). For the amount of effort, only modest gains were made. The urinary sodium was reduced to less than 75 mEg/day in 12.5% for both A and B groups compared to 60% in group C. The real reason for all of this, a reduction in blood pressure, was insignificant in all three groups. Still feedback may be a useful adjunct to other interventions in the elderly.

Feedback via home blood pressure monitoring may be rewarding, but the value rapidly diminishes unless professional supervision and positive reinforcement are continued.(42) Similarly, studies in which pharmacists(43) or nursing personnel(44) employed various compliance interventions indicated that, although initially successful, such methods often fail once close supervision is discontinued. Successful interventions should be continued indefinitely.

One simple and inexpensive approach to improving appointment keeping was evaluated by Takala and his colleagues.(45) They randomly allocated 202 Finnish hypertensives to an ordinary versus a "reorganized" treatment group. The latter group received written instructions after verbal instructions, a personal blood pressure follow-up card or diary, and a postcard reinvitation for missed appointments. The other group received only verbal instructions, and missed appointments were rescheduled only if the patient took the initiative to call. At the end of one year, the ordinary treatment group had a dropout rate of 19% compared with a 4% rate in the reorganized treatment group. Only 73% of the ordinary treatment group achieved goal blood pressure control, compared with 95% of the reorganized group ($P<0.01$). In our own clinic we have found that a phone call initiated by our clerical staff, with a postcard reinvitation yielded better results than a postcard alone, particularly when the patient selected a time from several choices offered.

Summary

In summary, it is important to expect and promote an attitude of shared responsibility between the physician and the elderly patient (or family) in an effort to achieve mutually shared goals. These goals should reflect the patient's values and desired outcome for therapy. The responsibility and role of the patient, the physician, and perhaps "significant others" should be explored. Patient participation in the health care plan or its subsequent modification should be invited. The cornerstone of an effective therapeutic partnership is a physician-patient relationship founded on mutual respect and understanding. A verbal contract, capped off with a warm handshake in this setting, may do more to foster a desired behavior in the patient than any other intervention.

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