The Gary Friedman Symposium

On May 11, 1998, a well-attended affair was held at the University of California in Berkeley, entitled: Gary Friedman at the DOR: 30 Years (and Counting)—A Celebration of a Career.

The triggering event for the celebration was the end of Gary Friedman's seven-year term as Director of the Kaiser Permanente Medical Care Program Division of Research (DOR) in Oakland. The program included six Scientific Presentations, each of which emphasized Gary's role as an initiator of scientific research and as a mentor of developing researchers. They also serve as an admittedly incomplete catalog of the epidemiologic oeuvre of the DOR over the past few decades; for this reason and because of scientific interest in the presentations, it was decided that publication of manuscripts based upon these talks in The Permanente Journal *would be of value. Five of the six presenters (including Gary) have submitted the manuscripts published here. Based upon somewhat informal talks, they should not be considered comprehensive, fully referenced reviews of the topics. Some anecdotal material relevant to the occasion was left in the manuscripts by several of the presenters. This deserved tribute to one of Kaiser Permanente's (KP's) most distinguished physicians (see biography) should interest and give pride to the* Journal's *readers.*

We hope it will also encourage others to submit original research articles to The Permanente Journal. *The work of Gary and his colleagues is an excellent example of the important discoveries that can accrue when clinicians analyze their practices in a rigorous fashion and share their findings with others.*

— Arthur L. Klatsky, MD, and
Mary Durham, PhD, Associate Editors

> *"Gary's very productive study[1] resulted in published articles about lung function,[2] psychological traits,[3] coffee,[4] medical history questions,[5] and the first report of the leukocyte count as a heart attack predictor."[6]*

Illegal, Immoral, or Bad for the Heart?
by Arthur L. Klatsky, MD

Introduction

It is a great pleasure and honor to be a speaker at this Symposium. In 1971, 10 years after I started cardiology practice with The Permanente Medical Group, Gary Friedman invited me to become a clinical associate in a National Heart Lung and Blood Institute application entitled "Predisposing Factors for Myocardial Infarction and Sudden Cardiac Death." It proved to be an event which changed my life. His invitation led to an exciting and personally very fulfilling second career in epidemiology, for which Gary's guidance, tolerance, and generosity are substantially responsible. He has been and remains a marvelous mentor.

First Alcohol-Coronary Heart Disease (CHD) Study

The essential and—at the time, novel—concept of the study was to use computer matching to find controls. Gary realized this possibility inherent in the existence of hundreds of thousands of multiphasic health checkup (MHC) records. This incredibly rich epidemiologic data base was created through the work of Dr. Morris Collen, who, among his many distinguished accomplishments, was the founder and first Director of the DOR. The matching execution was done by Abraham Siegelaub, who retired after a long, active DOR career and died several years later.

Hundreds of items (history questions, health measurements, lab tests) were screened. Gary called the study a fishing expedition, but I think the hypothesis was that new predictors would be found. This hypothesis was amply fulfilled—Gary's very productive study[1] resulted in published articles about lung function,[2] psychological traits,[3] coffee,[4] medical history questions,[5] and the first report of the leukocyte count as a heart attack predictor.[6] As we surveyed the data, an inverse relationship of coronary risk to alcohol drinking habits was one of the more striking findings. Gary very generously suggested that I write the first report of prospective data suggesting that nondrinkers were apparently at higher CHD risk. Thus, an article appeared in the *Annals of Internal Medicine* in 1974, reporting a significantly lower myocardial infarction (MI) risk among alcohol drinkers, compared to abstainers.[7]

There were 464 patients with a first MI. All had a prior MHC exam. The computer selected a "risk control" group well matched to each case for demographics and seven established coronary risk factors; and an "ordinary control" group matched only for age, race, and sex. Thus it was possible to ascertain whether a predictor was associated with or independent of the established risk factors. The important smoking-drinking interaction was recognized. In retrospect, lack of control for smoking was probably a major reason why prior studies failed to

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recognize this inverse alcohol/MI relationship. Results stratified by smoking habit were graphically presented (Fig. 1). Since this was the first published epidemiologic report of this finding and no mechanism was apparent, interpretation was cautious. Nine possible (mostly spurious) explanations were discussed, only one of which was a protective effect of alcohol.

Since then dozens of epidemiologic studies, including further Kaiser Permanente studies, have almost unanimously found that lighter drinkers are at lower coronary heart disease (CHD) risk than abstainers (both lifelong and former drinkers). Plausible mechanisms have been demonstrated, most notably that alcohol raises the coronary protective high-density lipoprotein cholesterol (HDL). Antithrombotic effects of alcohol may also be involved. Most scientists now accept this as a probable causal relationship. Benefit of lighter drinking for persons at coronary risk has found its way into U.S. and U.K. governmental advice to the public. Current debate is largely focused on possible additional benefits in specific beverages (wine, beer, liquor), and how

best to advise the public. Due to extensive lay media reporting, much of the public is aware of this relationship. A 1995 publication commemorating the 25th anniversary of the National Institute of Alcohol and Alcohol Abuse[8] cited the 1974 publication as one of 16 "seminal" articles in alcohol research.

This got us started in alcohol-health research, and led to a 20-year series of grants from the Medical Advisory Board of the Brewers Association of America and later from the Alcoholic Beverage Medical Research Foundation. These resulted in many reports. Over the years major roles were fulfilled by Abraham Siegelaub, Mary Anne Armstrong, and Harald Kipp.

Alcohol-Hypertension Association

One of the first reports from these studies was a 1977 NEJM article showing association of heavier drinking with hypertension.[9] This cross-sectional analysis showed age adjusted mean systolic and diastolic pressure in three racial groups according to usual drinks/day (Fig. 2). Hypertension prevalence was approximately doubled in
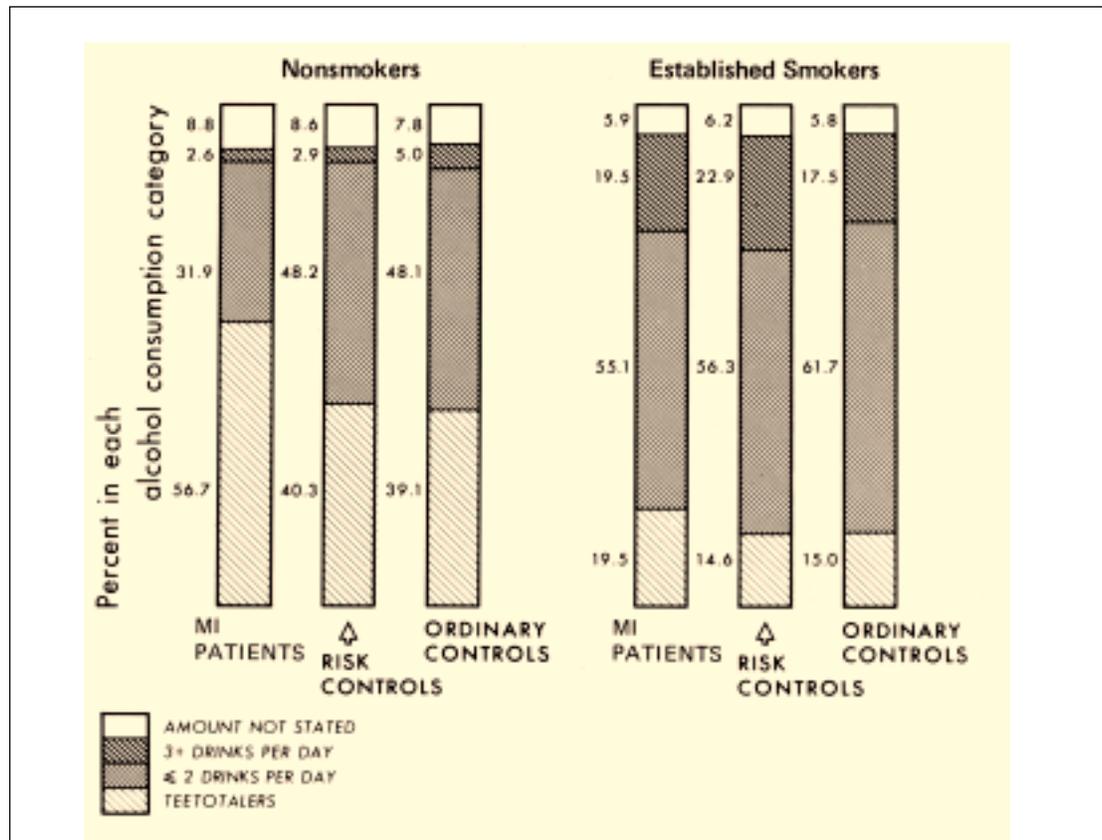

Fig. 1. The relation of alcohol consumption to cigarette smoking in myocardial infarction (MI) patients and both control groups. The nonsmokers include 113 MI patients, 129 risk controls, and 179 ordinary controls. The established smokers include 185 MI patients, 192 risk controls, and 120 ordinary controls. Reproduced from Klatsky et al.[10] by courtesy of the editors of the *Ann Intern Med.*

the heaviest drinkers. Direct cross-classifications showed independence from several potential confounders.

This was one of the first analyses of the alcohol-blood pressure relationship and remains one of the largest. By now dozens of cross-sectional and prospective epidemiologic studies, including additional Kaiser Permanente studies, have solidly established an empirical alcohol-hypertension link. These are supported by intervention studies showing blood pressure changes in several days to weeks with drinking or abstinence, with no convincing evidence that confounding is responsible. A mechanism has not been established although some data suggest a centrally mediated sympathetic nervous system action. The fact that explanations remain speculative is the only major deficiency in the case for causality.

Public Affairs Aspects

From the outset we had public affairs rewards and problems related to reporting benefits of light/moderate alcohol drinking. The major public health problems related to alcohol drinking are the adverse effects of heavier uncontrolled drinking. But it has always been widely apparent lighter drinking had few risks. No one expressed it better than Abraham Lincoln, who, more than 150 years ago, in a speech to a temperance society said:

"It is true that many were injured by intoxicating drink, but none seemed to think the injury arose from the use of a bad thing, but from the abuse of a good thing."

As Gary and I were flying to Atlantic City for the first public presentation of the alcohol-CHD data, we had a drink with dinner. Gary said to me, "we may have to be careful about drinking in public after our presentation, because we'll be accused of wanting to justify our bad habits."

Indeed we have been attacked over the years—not for our personal habits, but for possible bias related to our funding. The obvious harmful effects of alcohol make it difficult for many to accept the concept of possible benefit from lighter drinking. The attacks were bothersome, but Gary—as always—was a calming influence. The funding sources of the early studies became useful in rebuttal of suggestions of possible bias in our work. The apparent beneficial effect of lighter drinking in CHD was uncovered by work supported by the NIH, while the apparent harmful effect on blood pressure resulted from work indirectly supported by beverage industry funds. Of far greater importance in—I think—our success in maintenance of a reputation for honest reporting has been Gary's richly deserved reputation as in investigator of absolutely impeccable integrity.

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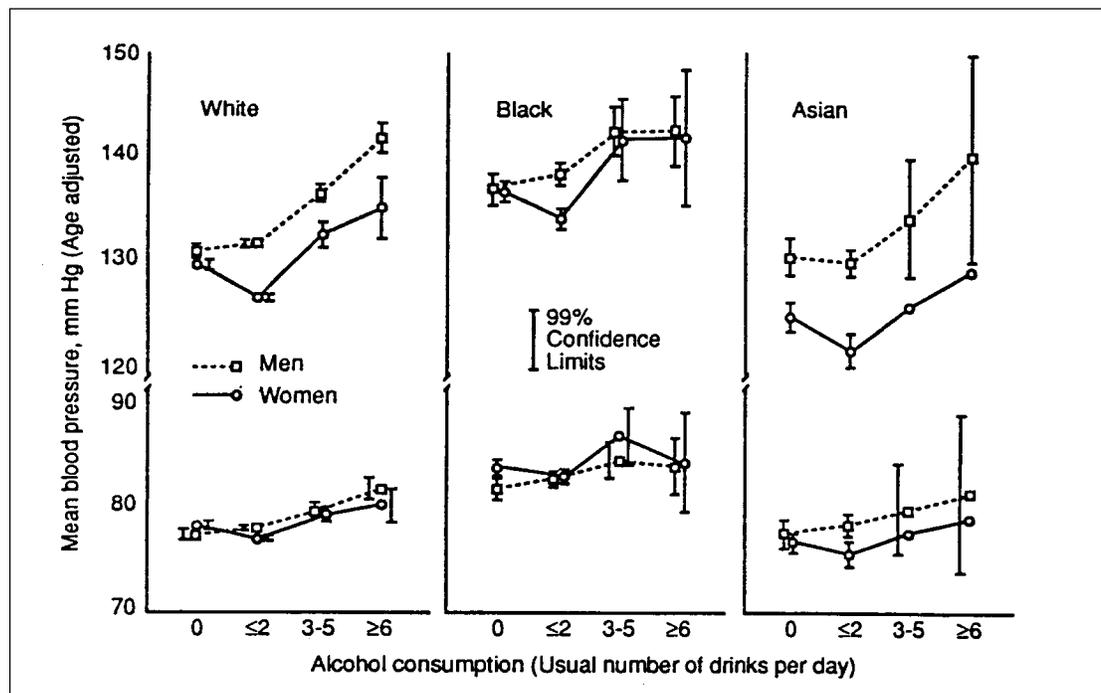

Fig. 2. Mean systolic blood pressures (upper half) and mean diastolic blood pressures (lower half) for white, black, or Asian men and women with known drinking habits. Small circles represent data based on fewer than 30 persons. Reproduced from Klatsky et al.[9] by courtesy of the Editors of the *N Engl J Med.*

Alcohol-Mortality Relationship

In returning to the alcohol CHD story, I want to briefly describe one additional report based upon the 1964-68 data base. This was a 10-year follow-up of four matched groups of 2015 persons. An excellent match was found for each person reporting 6+ drinks per day among nondrinkers, drinkers of <2 drinks/day, and a daily drinker of 3-5 drinks. The data, reported in the *Annals of Internal Medicine* in 1981,[10] showed a J-shaped to-tal mortality relation to alcohol, and a U-shaped curve for cardiovascular deaths. The nadirs of the mortality curves were due mostly to lower CHD death rates in lighter drinkers; the increased risk of heavier drinkers was due to a variety of causes. By the time of this report, some data about HDL cholesterol and antiplatelet effects of alcohol had appeared; these possible mecha-nisms for the alcohol-CHD relationship were mentioned.

Alcohol Data In a 1978-1985 Cohort

A special alcohol research questionnaire was ap-pended to the MHC examination from 1978 through 1985 at Oakland, and from 1978 through 1980 in San Francisco. Almost 129,000 persons satisfactorily com-pleted this questionnaire. Lighter drinking was now subdivided into 3 groups and data were gathered about wine, liquor, and beer use. Nondrinkers received ques-tions about past drinking, reasons for abstinence or quitting, and maximum past amount for ex-drinkers. Alcohol questionnaire responses were reasonably com-parable to data from a subset who also gave seven day recall information about alcohol in a study performed by Lorraine Midanik.[11] We derived definitions of "pref-erence" based upon usual number of days/week each beverage (wine, liquor, beer) was taken. A report of correlates of usual alcoholic beverage preference[12] de-tailed major differences between the groups, indicating that the lifestyle habits of wine preferrers were healthi-est and those of liquor preferrers least healthy.

The long range objective was study of relationships of drinking behavior to a variety of health measure-ments and outcomes. Prospective alcohol related re-ports included analyses of pancreatic,[13] breast,[14] pros-tate,[15] and large-bowel cancer;[16] total hospitalization days,[17] changes in drinking,[18] liver cirrhosis,[19] cerebrovas-cular disease,[20] supraventricular arrhythmias,[21] total mortality,[22] unnatural deaths,[23] and, of course CHD.[24-27] New cross-sectional analyses of the alcohol-hyperten-sion relationship[28] and the alcohol-smoking association[29] were also published.

The first CHD study based upon the new data set was a prospective analysis of 756 hospitalized persons.[24] This multivariate analysis showed that past drinkers and very infrequent drinkers (< once per month) had CHD risk similar to that of lifelong abstainers. Lower risk was found at higher drinking levels, independent of baseline CHD risk or symptoms. Choice of beverage had no major independent relationship in the entire group and at specific drinking levels.

The "Sick-Quitter" Hypothesis

In 1988 a major counter hypothesis was forcefully pre-sented in a *Lancet* article[30]—with editorial support and wide media publicity. It has been called the "sick-quit-ter hypothesis." Briefly stated, it says that lighter drink-ing is not really protective against CHD, but that ab-stainers are at higher risk because of more baseline dis-ease in this group. Previous studies, including our ear-lier ones, were cited as defective because they did not separate nondrinkers from ex-drinkers. This, of course, was not the case in our new data base. Gary pointed out that this controversy was a break for us, because it afforded a good opportunity for rebuttal by creating interest in new studies. Others obviously felt the same way, because a number of reports soon appeared which separated out ex-drinkers and controlled for baseline disease. These reports, in my opinion,[31] have put the "sick-quitter" hypothesis firmly to rest. In 1990 we pre-sented a prospective report of alcohol relation to 1002 cardiovascular deaths, with special emphasis upon ex-drinkers.[25] Ex-drinkers and very infrequent drinkers were at risk similar to abstainers in adjusted analyses of all cardiovascular or CHD deaths. Ex-drinkers were at higher risk only for noncardiovascular causes, and quitting for medical reasons enhanced this risk. Reasons for quitting or baseline CHD risk had little relationship to CHD risk. These data were interpreted as suggesting that the lower risk of drinkers for CHD was not due to selective absti-nence by high risk persons.

The Role of Beverage Choice

Almost everyone is familiar with the concept of the "French Paradox," which was widely popularized by *60 Minutes* telecasts in 1991 and 1995. The "paradox" is the low CHD mortality in France despite a CHD risk profile similar to other Western countries. This hypoth-esis has been supported by several international com-parison ecologic studies, going back to a 1979 report[32] of an inverse relationship between national wine con-sumption and CHD mortality. More recently, it has been shown that France is an outlier on graphs of national saturated fat consumption and CHD mortality, unless corrected for wine intake.[33]

Little is new under the sun. Actually, the first presen-tation pertinent to the "French Paradox" was in 1819 by Dr. Samuel Black,[34] an Irish physician with a great in-terest in angina pectoris and of considerable percep-tion with respect to epidemiologic aspects. His delight-fully Francophile explanation of the disparity in CHD

between Ireland and France, attributed the low French angina prevalence to "the French habits and modes of living, coinciding with the benignity of their climate and the peculiar character of their moral affections."

The recent studies, plus the discovery of antioxidant phenolic compounds in red wine, have led many to believe that alcohol is protective against CHD, but that

Table 1. Adjusted RR CHD* by Total Alcohol

Alcohol Use	Men RR (CI)	Women RR (CI)
Abstainers#	1.0 (ref)	1.0 (ref)
Ex-drinkers	1.0 (0.8-1.2)	1.1 (0.8-1.5)
Infrequent**	0.9 (0.9-1.1)	1.- (0.9-1.2)
usual drinks/day		
<1	0.9 (0.8-1.1)	0.8 (0.7-1.0)[a]
1-2	0.8 (0.7-0.9)[b]	0.6 (0.5-0.8)[c]
>3	0.7 (0.6-0.9)[c]	0.6 (0.4-0.9)[b]

* 3931 persons hosp for CHD (among ~ 129,000)

\# lifelong (4125 men, 11,373 women)

** less than once/month

a=p<0.05; b=p<0.01; c=p<0.001

Table 2. Adjusted RR* CHD by Total Wine, Liquor, Beer

Group	Wine	Liquor	Beer
total alcohol not controlled			
Both sexes	0.8[b]	0.9[b]	0.7[c]
Men	0.9	0.9	0.7[c]
Women	0.7[b]	0.9	0.7
total alcohol controlled			
Both sexes	1.0	1.0	0.9
Men	1.0	1.0	0.8[a]
Women	0.9	1.3	1.0

*proxy variable representing drinks/day of beverage type

a=p<0.05; b=p<0.01; c=p<0.001

red wine is more protective than other alcoholic beverages. Prospective population studies, on the other hand, show no consensus, and suggest that each beverage type is protective.[35] This controversy led us to study this aspect. We first examined CHD mortality by studying risk for persons who took almost all of their alcohol in the form of one beverage type.[26] These preference groups represented only a fraction of the CHD deaths, and there were major user differences between the groups. All beverage types were protective, but wine and beer preferrers were at lower risk than liquor preferrers—this difference was statistically significant only for wine preferrers. There was no difference in risk between persons who took red wine and those who took other types of wine.

We recently reported CHD hospitalization data with a much larger group of cases.[27] As in all previous Kaiser Permanente studies, total alcohol intake was inversely related to CHD risk (Table 1). By assigning a proxy variable to use of wine, liquor or beer, we were able to utilize all beverage choice data. Again, each beverage type was protective, but beer use appeared most protective in men and wine (both red and white) in women (Tables 2 and 3). We concluded that the major benefit was from alcohol and that user differences and drinking patterns were most likely to be responsible for the beverage type disparities. I think

Table 3. Adjusted RR* CHD Among Persons# Taking 1-2 Drinks/Day

Beverage Type			
Group	Wine	Liquor	Beer
Both sexes	1.0	1.0	0.7[a]
Men	1.0	1.0	0.7[a]
Women	0.7	1.0	0.5
Type of Wine			
	Red	White	R&W	Other
Both sexes	1.3	1.0	0.9	0.7
Men	1.3	1.1	0.9	1.0
Women	0.5	0.8	0.7	0.6

*using proxy variable representing drinks/day of type

\# n = 13,512 men reporting 1-2/day, 530 of whom were later hospitalized for CHD; and 9896 women reporting 1-2 drinks/day, 149 later hospitalized for CHD

a=p<0.05

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clinical contributions

"We concluded that the major benefit was from alcohol and that user differences and drinking patterns were most likely responsible for the beverage type disparities."

that this view has become the prevailing current assessment of many workers in the field, but, as Yogi Berra's much quoted wisdom goes, "it isn't over until it's over."

Conclusion

We remain active in the alcohol-epidemiology field. The major current effort is a study of alcohol and stroke. Plans include further exploration of beverage choice and various health outcomes. I certainly hope that my association with Gary will continue for many years. It would be highly appropriate to have a drink to this wish, but I'll have to be content with answering the query: "Is everything one enjoys illegal, immoral, or bad for the heart?" The answer is "not quite." ❖

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The CARDIA Study and the Development of Clinical Research at the Division of Research

by Stephen Sidney, MD, MPH

One of Gary Friedman's legacies to the Division of Research (DOR) was the development of a clinical research unit. Prior to 1984, the DOR (then known as Medical Methods Research) had been involved in few externally funded studies involving the clinical examination of research subjects, the most notable of which was a study of female twins, funded by NHLBI and headed by Gary. In December 1983, that changed with the funding of the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Gary was the principal investigator and led the writing of a successful application for Kaiser Permanente (KP) to be one of the four field centers for this study. CARDIA was initially funded for a period of five years with a baseline and a two-year followup examination and with the primary aims: 1) to determine the distribution of coronary heart disease risk factors in a biracial cohort of men and women aged 18-30 years at entry; and 2) to identify habits and behaviors that are associated with both initial levels and later changes in these risk factors.

Our initial plan was to conduct the clinical examinations for this study in the multiphasic health checkup area of the Oakland KP Medical Center, but we soon realized that this facility would not be adequate. The problemsolving process led us to develop research clinic space in the old DOR building on Piedmont Avenue. In February 1985, clinic equipment and supplies began to arrive at the DOR in preparation for the baseline exam startup scheduled to take place in the late spring—a low-temperature freezer, centrifuge, pulmonary function and exercise treadmill testing equipment, needles, syringes, food models, etc. It was both an exciting and chaotic time for us.

At the baseline examination conducted for a year in 1985-86, 5115 participants were recruited into the 4 clinical centers (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) with 1426 recruited at Oakland, making it the largest center. The participants were 18-30 years of age, with relatively equal numbers of African Americans and whites, men and women, ages 18-24 and 25-30 years, and education <12 years and ≥12 years. The success of the study (high quality data and 91% cohort retention at the two-year follow-up) led to continued funding. Five examination cycles have been completed (baseline and 2-, 5-, 7-, and 10-year follow-up exams), and a 15-year follow-up examination is planned for the year 2000-01. Retention has remained very high for this relatively young and mobile cohort with nearly 80% of the cohort returning for the 10-year follow-up exam.

The longitudinal study of cardiovascular risk factors in the CARDIA Study group has yielded very interesting findings. A sampling of these findings is shown in Figs. 1 through 4. Fig. 1 shows the mean cumulative weight change over time, one of the more dramatic findings from the CARDIA Study. The mean 10-year weight change ranges from a 15.7-pound increase in white women to a 25.4-pound increase in African American women. Fig. 2 suggests one of the reasons for this marked weight gain. Physical activity score, reflecting the frequency and intensity of participation in 13 different kinds of activity during the past year, decreased substantially and fairly consistently over 10 years with a mean decrease of about 20% in men and 25% in women. Fig. 3 demonstrates relatively small 10-year changes in systolic blood pressure (SBP). All race/gender groups show a decrease in SBP between the baseline exam and the two-year follow-up, a

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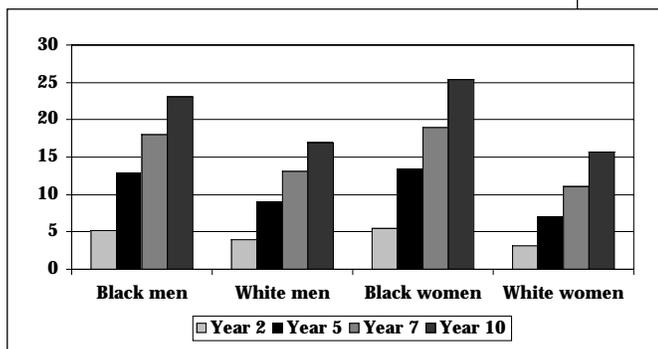

Fig. 1. Ten-year trend in mean cumulative weight change (lb) by race/gender
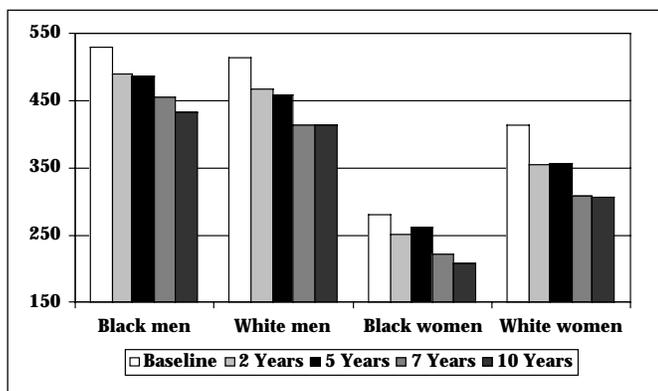
Fig. 2. Ten-year trend in mean physical activity score by race/gender

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Fig. 3. Ten-year trend in mean systolic blood pressure (mm Hg) by race/gender

Fig. 4. Ten-year trend in mean LDL cholesterol (mg/dL) by race/gender

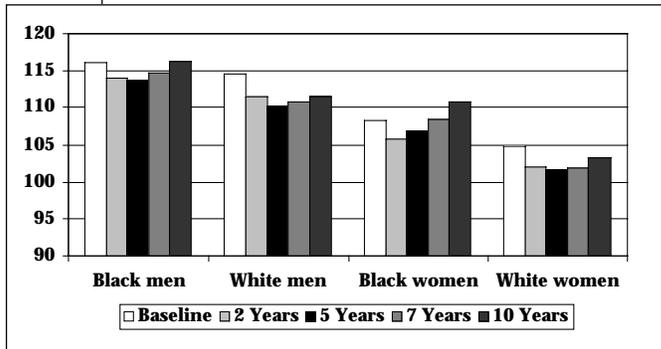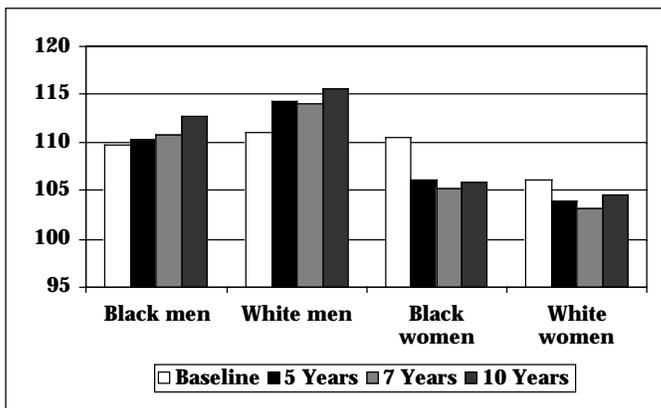lesterol has trended upward in men and downward in women since the baseline examination.

The observation that LDL cholesterol is actually decreasing in women (and not increasing dramatically in men) in spite of large weight increases might seem surprising to some. One of the strengths of the CARDIA Study is that the longitudinal measurement of many factors that influence cardiovascular risk, and the aging of the younger part of the study cohort has allowed us to understand to a great degree how this perplexing situation has occurred. CARDIA is the first study to document directly the impact that secular trends are having on individual changes in LDL cholesterol level with age. Two concepts of group change need to be understood:

1) Cohort (or aging) change, which is change occurring in a measurement over time associated with aging of the study cohort; and

2) Secular change, which is the component of change occurring in a measurement over time that is not associated with aging, but is associated with overall societal trends.

In the CARDIA Study, Bild et al. examined seven-year secular trends by comparing older participants at the baseline CARDIA examination (ages 25-30 year, N=2788) with younger CARDIA participants who aged into the 25-30 year group at the seven-year follow-up exam (ie, those who were 18-23 years old at the baseline exam in 1985-86 became 25-30 years old at the seven-year follow-up exam in 1992-93, N=1395).[1] Comparison of these two groups (those who were 25-30 years-old at baseline and those who were 25-30 years old at the seven-year follow-up) provides information on the secular influences that have caused changes in the characteristics of 25-30-year-olds at these two points in time. Table 1 shows the secular percentage changes in LDL-cholesterol, body weight, and Keys score. The Keys score predicts cholesterol change based on changes in dietary fat and cholesterol and was measured from dietary data collected at both points in time. We see that a secular decrease in LDL cholesterol occurred during this time period, ranging from 5.2% to 8.9%, in the setting of a secular increase in body weight (ranging from 5.3% to 6.9%) and a secular decrease in Keys score (ranging from 9.5% to 15.2%). We conclude that the secular decrease in LDL cholesterol offsets the expected increase in LDL cholesterol with age and increasing weight and that this decrease was probably due to secular dietary changes that lowered lipids.

As the CARDIA Study prepares for a 15-year follow-up exam, the participants are still too young to experience many incident events of atherosclerotic cardiovascular disease. However, it has only recently become clear that the presence of subclinical cardiovas-

finding common to most observational epidemiologic studies which is probably related to acclimatization of the participant to the research environment. Mean SBP at the 10-year follow-up exceeds the baseline SBP only for African American women, is nearly equal for African American men, and has not yet returned to baseline for white study participants. Fig. 4 demonstrates divergent trends in mean low-density lipoprotein (LDL), the "bad" cholesterol, in men and women. LDL cho-

Table 1. Seven-year secular trends in LDL cholesterol, body weight and Keys score (% change)*				
	Black men	White men	Black women	White women
LDL cholesterol (mg/dL)	- 8.9	- 5.2	- 9.2	- 5.5
Body weight (lb)	7.2	5.3	5.3	8.5
Keys score	-10.1	-15.2	- 9.5	-16.5

*Calculated comparing participants ages 25-30 years in 1985-86 (n=2788) with those aged 25-30 years in 1992-93 (n=1395).

cular disease can be quantified noninvasively in a substantial proportion of the population in the age spectrum represented by the CARDIA Study population. For example, coronary artery calcium can be quantified quickly and noninvasively by electron beam computed tomography (EBCT) and has been found to correspond to the quantity of coronary plaques and the probability of significant disease as assessed by angiography. The Oakland and Chicago centers participated in a CARDIA EBCT substudy that was conducted during 10-year follow-up exams. In the 443 CARDIA Study participants, coronary artery calcium was detected in 40% of African American men, 46% of white men, 37% of African American women, and 17% of white women.[2] The high prevalence of subclinical CVD in this population of young adults is not surprising, reflecting the fact that atherosclerosis is a lifelong process that is highly prevalent in this country. Plans for the 15-year follow-up exam include the assessment of atherosclerosis in the carotid artery of all study participants using ultrasound imaging.

Gary remained the principal investigator of the CARDIA Study until he was awarded an Outstanding Investigator Grant from the National Cancer Institute in 1991. During his tenure as the Principal Investigator, he wrote two papers based on the CARDIA data. The first was a descriptive paper about the design of the CARDIA Study with a report of the recruitment experience for the baseline examination and some of the sociodemographic and risk factor characteristics of the study cohort.[3]

The second paper has a story to go along with it because it represents part of a longer story about the pioneering aspect of Gary's work, of his being the "discoverer" of epidemiologic findings that other researchers later replicated and verified. In this case, it is the story of the leukocyte count (white blood cell count) and coronary artery disease. In 1974, *The New England Journal of Medicine* published a paper by Gary, Art Klatsky, and Abe Siegelaub showing that leukocyte count predicted the development of first acute myocardial infarction.[4] In an accompanying editorial, Dr. Henry Blackburn, a noted cardiovascular epidemiologist, expressed the importance of search for new indicators of coronary risk and said about Gary's paper, "The Kaiser group has gone fishing and caught an interesting specimen, the leukocyte count."[5] Gary's second CARDIA paper, published in 1990, was an analysis of association of the leukocyte with sociodemographic and cardiovascular risk factors, and represented his continued interest in the relationship of the leukocyte to cardiovascular risk.[6] Why would the leukocyte count be associated with coronary heart disease (after accounting for

the effects of cigarette smoking)? A recent line of investigation suggests that inflammation and evidence of past infection with one of several agents (*Chlamydia pneumoniae,* cytomegalovirus, and herpes simplex virus type-1 (HSV-1) are associated with increased risk of atherosclerosis.[7-10] Cytokines have been shown to mediate many of the changes induced by inflammation, including atherogenic alterations in lipid metabolism.[11] Perhaps this might be the link between the leukocyte count and cardiovascular disease risk, ie, that the leukocyte count is, to some degree, a marker of inflammation. We should be able to examine this question, perhaps closing the loop of causation on Gary's finding from nearly a quarter century ago.

The seed sown by Gary in the start up of the CARDIA study has grown into the implementation of many clinical research studies at the DOR, and the development of a large clinical research facility. These studies account for about 20 to 30 percent of the annual DOR research budget. The growth of clinical research activity has been particularly rapid during Gary's tenure as director, and is one the many legacies of his research career at the DOR . ❖

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"The high prevalence of subclinical CVD in this population of young adults is not surprising, reflecting the fact that atherosclerosis is a lifelong process that is highly prevalent in this country."

"The Kaiser group has gone fishing and caught an interesting specimen, the leukocyte count."[5]

"A recent line of investigation suggests that inflammation and evidence of past infection with one of several agents (Chlamydia pneumoniae, cytomegalovirus, and herpes simplex virus type-1 HSV-1) are associated with increased risk of atherosclerosis."[7-10]

"Sensitive" and "Specific" Epidemiologic Studies: The Division of Research of the Kaiser Permanente Medical Care Program

by Noel S. Weiss, MD, DrPH

> *"There are a number of strategies available to epidemiologists to increase the specificity and sensitivity of their investigations, the use of which generally makes the results they obtain more valuable."*

> *"Inaccuracy in the assessment of either exposure or outcome status will lead to a biased result. The DOR has thought to minimize error by means of its careful data collection methods."*

As critics of epidemiologic research are all too eager to point out,[1,2] this type of research can lack both "specificity"—it can erroneously observe an association—and "sensitivity"—it can fail to identify an association that truly is present. There are a number of strategies available to epidemiologists to increase the specificity and sensitivity of their investigations, the use of which generally makes the results they obtain more valuable. Nearly all of these have been employed commonly by Gary Friedman and his colleagues at the Division of Research (DOR), which is one of the reasons their work is valued so highly.

Minimization of Measurement Error

Inaccuracy in the assessment of either exposure or outcome status will lead to a biased result. The DOR has thought to minimize error by means of its careful data collection methods. In addition, when error is unavoidable it is recognized by the investigators, and the data are interpreted accordingly. For example, in his case-control study of risk factors for multiple myeloma,[3] Gary Friedman examined medication use that occurred no more recently than a reference date set six months prior to the date of diagnosis among cases (and a corresponding point in time in controls). This was done in an effort to reduce the chance that an early manifestation of not-yet-diagnosed multiple myeloma led to taking a particular drug, and thus created a spurious association. In this study, an association was found with use of the analgesic, propoxyphene; 41.3% patients had taken this drug before the reference date vs. 33.6% of controls (odds ratio = 1.44). However, nearly the whole of the association was due to propoxyphene use in the two years prior to the reference date (odds ratio = 2.1); the odds ratio associated with propoxyphene use before that time was only 1.17. Gary Friedman duly warned his readers that such a pattern of odds ratios was unlikely to reflect a causal role of propoxyphene use on the risk of multiple myeloma. Rather, this pattern was more consistent with "reverse" causality, that is, disease giving rise to drug use. He realized that for this drug, the reference date simply had not been set far enough back in time prior to diagnosis.

Exposure Subclassification

Generally, not all users of a drug or other therapy that alters the incidence of a given outcome are at equal risk of that outcome. The risk may vary by dose, duration, or recency of the therapy, for example, and the DOR studies of the effects of therapy consistently have been characterized by their search for such heterogeneity. An important extension of this work occurred in the DOR evaluation of the efficacy of various screening modalities against mortality from colorectal cancer.[4-6] Their case-control studies of sigmoidoscopy, fecal occult blood testing, and digital rectal exam took account of the fact that the duration of the screening benefit cannot exceed that period of time that a tumor is clinically occult and yet detectable by a given test. By examining differences between cases and controls in the receipt of screening in different periods of time extending backwards from the time of diagnosis, they could explore the possibility of a transient benefit associated with screening.

Disease Subclassification

Every disease has multiple causes, and often at least some of these causes can act separately from one another. Sometimes, a particular cause operates in a way that results in specific manifestations that differ to some extent from those produced by other causal factors for the same disease. For example, occupational exposure to chloromethyl ether appears to predispose only to one histologic type of lung cancer, small cell cancer, and not others.[7]

In their study of gastric cancer in relation to prior infection with *Helicobacter pylori*,[8] DOR investigators acknowledged this possibility by subdividing cases according to anatomic location within the stomach. No association with *H. pylori* infection was observed for tumors of the gastroesophogeal junction, in contrast to a 3.6-fold increased risk of other gastric cancers. Had they not disaggregated the case group, an overall relative risk would have been obtained that would not have reflected the size of the association with either cancer subsite.

Conclusion

Many of the questions that epidemiologic studies address require a great deal of careful handling in order to maximize the chances of finding an association when one is there and of not finding one when there truly is none present. Gary Friedman and his colleagues at the Division of Research have set an excellent example for the rest of us to follow in designing such sensitive and specific studies. Because

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these studies have had such a large impact, the scientific community and other consumers of DOR research are hoping that both Gary and the DOR, together and separately, will continue to set this kind of example for a good while longer. ❖

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Screening for Colorectal Cancer: Research Contributions of The Permanente Medical Group

by Joe Selby, MD, MPH

Screening for colorectal cancer has been a topic of exceptional interest to clinician researchers in The Permanente Medical Group since the early 1950s. Rigid sigmoidoscopy was employed in at least two medical centers at that time[1] and became a part (albeit an optional part) of the multiphasic health checkup from its earliest days. The work of a number of investigators has added to and, in several cases, led development of public policy on screening for this common malignancy. Gary Friedman had a hand in many of these studies, as we shall see.

The Multiphasic Evaluation Study

This important study was an ambitious investigation,[2,3] using randomized trial methods, to determine if periodic multiphasic testing could reduce mortality in healthy, middle-aged health plan members. Beginning in 1964, nearly 11,000 members aged 35-54 years were randomized to either a group study (N=5156) that was contacted annually by phone and urged to schedule a multiphasic health checkup annually, or to a control group (N=5557) who received no telephone calls but were free to schedule multiphasic checkups as they wished. Annual contact of intervention group subjects continued for ten years. The study was not intended or designed to test the efficacy of sigmoidoscopy. Rather, total mortality was the chief endpoint. The architects of the study, including Drs. Morris Collen and Gary Friedman, also designated a subgroup of causes of death as "potentially postponable deaths" and hypothesized that the reduction in mortality would be principally among these causes. Because sigmoidoscopy was an optional part of the multiphasic health checkup, death from colorectal cancer was included, along with deaths from cancers of the breast, uterus, cervix, prostate and kidney, from hypertension, hypertensive heart disease, and hemorrhagic cerebrovascular disease as potentially postponable deaths.

After 16 years of follow-up, mortality from potentially preventable causes was 30 percent lower in the study group, and approximately half of this reduction was due to fewer deaths from colorectal cancer (Table 1).[3] Because colorectal cancer was not the focal point of the Multiphasic Evaluation Study, Friedman et al dedicated a relatively modest amount of space in their report to discussing details of the finding. They suggested that a specific trial of this question was needed to determine whether sigmoidoscopy indeed reduced mortality.

Despite these cautions, the Multiphasic Evaluation Study was embraced in the early 1980s by advocates of "evidence-based guidelines" as randomized trial evidence that sigmoidoscopy can lower mortality from colorectal cancer.[4,5] The American Cancer Society, among others, used the study to endorse periodic (every three years) sigmoidoscopy.[5]

Concerned that the full story may not have been told, Dr. Friedman and I began a further set of analyses of the Multiphasic Evaluation Study in 1985.[6] We reasoned

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"After 16 years of follow-up, mortality from potentially preventable causes was 30 percent lower in the study group, and approximately half of this reduction was due to fewer deaths from colorectal cancer (Table 1)."[3]

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Table 1. 16-Year Mortality in the Kaiser Permanente Multiphasic Evaluation Study

Cause of Death	Death Rates (per 1,000 for 16 years)		Chi-Square
	Study (N=5156)	Control (N=5557)	
Potentially postponable causes	15.0	21.5	6.26*
Cancer of colon & rectum	2.3	5.2	5.86*
Cancer of breast (women only)	4.1	4.3	0.04
Cancer of cervix and endometrium	1.0	0.9	0.01
Cancer of prostate (men only)	0.2	0.9	2.38
Cancer of kidney	0.2	0.7	1.59
Hypertension, hypertensive cardiovascular disease and hemorrhagic cerebrovascular disease with hypertension	4.7	7.2	2.92
Hemorrhagic cerebrovascular disease without hypertension	2.5	2.2	0.15
Other causes	98.9	94.7	0.46
All causes	113.9	116.1	0.71

*p<0.05

Table 2. Further analyses of colorectal cancer incidence and stage distribution, by anatomic location, from the Kaiser Permanente Multiphasic Evaluation Study

	Study	Control
Mortality (deaths per 1,000) with 18 yrs follow-up		
Cancers within reach of sigmoidoscope	1.4	2.7*
Cancers above reach of sigmoidoscope	4.1	4.9
Cumulative incidence (cases per 1,000) with 18 yrs follow-up		
Cancers within reach of sigmoidoscope	4.3	6.7*
Cancers above reach of sigmoidoscope	4.1	4.9
Case fatality rate (%)		
Cancers within reach of sigmoidoscope	32	41
Cancers above reach of sigmoidoscope	43	48

*p <0.10

that if sigmoidoscopy were responsible for the lowered mortality from colorectal cancer, the mortality reduction should principally be for cancers of the rectum or distal colon (ie, cancers within reach of the sigmoidoscope). We further suggested that sigmoidoscopy could lower mortality by either or both of two mechanisms. It could lower incidence of cancer (by detection and removal of adenomatous polyps), or it could improve the stage distribution of cancers. Finally, because the sigmoidoscopic examination was an optional part of the multiphasic, dependent upon scheduling by the patient and occurring at a separate later examination, we wanted to assure ourselves that there really was an excess of screening sigmoidoscopy in the study group.

After reviewing records of all incident cases of colorectal cancer and detailed chart abstraction forms from the entire cohort, we observed the following: 1) the mortality reduction in the study group was somewhat greater for cancers within reach of the sigmoidoscope than for cancers above reach of the sigmoidoscope (Table 2). Two-thirds of the reduction in mortality from distal colorectal cancers was due to lowered incidence; the remaining third appeared to be due to earlier detection with an improved stage distribution and lower case fatality rate. However, there was no difference between groups in removal of adenomas during the follow-up period. Thus, the incidence reduction can not comfortably be attributed to sigmoidoscopy.

In further analyses, only a small fraction of the cancers were detected by screening in either group and the study group's stage shift improvement was as great for cancers detected after onset of symptoms as for screen-detected cancers. Thus, it does not appear that screening sigmoidoscopy accounted for much of the stage shift either. When we tallied the total number of sigmoidoscopies in each group, the study group had only a slight excess of sigmoidoscopies and this was contributed by a very small group of individuals (N=212 excess persons) who heeded the telephone urgings meticulously and had, on average, 3.3 sigmoidoscopic examinations in the ten-year period. This small excess of screening would be expected to prevent less than one fatal cancer.

In summarizing, we could say only that the Multiphasic Evaluation Study had not been designed or sized to test the efficacy of sigmoidoscopy and its results should not be used as evidence either for or against sigmoidoscopic screening.

The U.S. Preventive Services Task Force

Dr. Friedman joined the U.S. Preventive Services Task Force in 1985. Shortly thereafter, he was asked to prepare a paper evaluating the evidence supporting inclusion of sigmoidoscopy in the periodic examination of healthy adults. I joined him in this effort,[7] reviewing the several descriptive studies that had reported the favorable stage distributions of cancers detected by screening sigmoidoscopy and jumped inappropriately to conclude that this earlier stage distribution was proof that screening sigmoidoscopy could save lives. We also re-

viewed the Multiphasic Evaluation Study and concluded that there was not sufficient evidence to support inclusion of sigmoidoscopy in the periodic health examination. We suggested further that, since a randomized trial of sigmoidoscopy was unlikely in the near future, controlled observational studies had the greatest potential for providing some evidence on its efficacy.

A Case-control Study of Screening Sigmoidoscopy

In 1982, Morrison discussed the potential of case-control studies for evaluating the efficacy of screening tests.[8] Noel Weiss carried the discussion and the theory further.[9] Gary was familiar with these papers and recognized that Kaiser was ideally suited to conduct a case-control study of the efficacy of sigmoidoscopy. Our cancer registry identified large numbers of colorectal cancers, along with their anatomic location and subsequent vital status. Medical records allowed us to ascertain exposure to screening sigmoidoscopy along with a variety of covariates. Moreover, substantial screening with sigmoidoscopy had occurred over the past 20 years, so that exposure was sufficiently frequent that a benefit would be detectable with a reasonable sample of cases and controls if it existed.

Funded by the National Cancer Institute, the study was undertaken in 1989. The case definition was fatal colorectal cancer arising within reach of the rigid sigmoidoscope. Controls were drawn from the health plan membership, were matched on age and sex to cases, and had to outlive the case and not die of colorectal cancer. A total of 261 eligible cases were identified. These were matched to 868 controls. A large deficit of exposure to screening sigmoidoscopy was observed among cases during the ten years preceding diagnosis of the fatal cancer. This yielded an odds ratio of 0.30, suggesting a 70% reduction in risk of fatal colorectal cancer associated with screening. After adjustment for a number of possible confounders, including personal and family history of colorectal cancer or polyps, exposure to other screening tests, and history of periodic health checkups, the odds ratio increased slightly to 0.41, still suggesting nearly a 60% risk reduction.

To determine whether this association might have been due to additional unmeasured self-selection factors, we studied an additional group of 268 patients who died of colorectal cancers arising above reach of the sigmoidoscope and a similar number of matched controls. For these cancers, sigmoidoscopy should offer no benefit. Any observed benefit would most likely be due to confounding by self-selection factors that made persons undergoing screening sigmoidoscopy less likely to develop or die from colorectal cancer. However, after adjusting for the same set of measured confounders, there was no

Table 3. Odds ratios (OR) for having at least one screening sigmoidoscopy in the ten years before case's diagnosis			
All cases within reach of rigid sigmoidoscope:			
Cases (N=261)	Controls (N=868)	Unadjusted OR (95%CI)	Adjusted OR* (95% CI)
24 (9%)	210 (24%)	0.30 (0.15-0.46)	0.41 (0.25-0.69)
All cases above reach of rigid sigmoidoscope:			
Cases (N=268)	Controls (N=268)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
54 (22%)	67 (27%)	0.80 (0.54-1.19)	(0.96 (0.51-1.50)

*Adjusted for personal history of colorectal cancer or polyps, familty history of colorectal cancer, number of periodic health checkups, and number of other colorectal cancer screening tests during the ten-year interval.

residual benefit in this group (Table 3). The striking difference in benefit between cancers within reach and those above the reach of the sigmoidoscope strengthened the inference that sigmoidoscopy was truly beneficial.

Another important finding of the study was the observation that a person's risk for developing fatal colorectal cancer remained extremely low for at least ten years following a negative sigmoidoscopy. This observation fit with what is known of the biology of colorectal cancer (ie, that cancer develops slowly from adenomatous polyps over a period of many years). However, it clashed with recommendations of the time that sigmoidoscopy should be performed every three years. A longer interval between screenings would make a sigmoidoscopy screening less costly as well as more acceptable to patients.

The findings from this study were published in *The New England Journal of Medicine* in 1992[10] and reviewed by the U.S. Preventive Services Task Force in 1994. On the basis of this study, the Task Force recommendation for sigmoidoscopy was upgraded from "insufficient evidence" (Grade C) to "fair evidence" (Grade B), meaning that the Task Force now supported screening with sigmoidoscopy. On the strength of this change, coverage for screening by sigmoidoscopy has now been added by HCFA for Medicare recipients and by many private insurers.

The CoCaP Program

The Permanente Medical Group took great pride in the recognition received by the case-control study. Having produced the evidence on efficacy, however, the Group was faced with a decision as to how it should respond to the study's findings. Although a few medical centers had sigmoidoscopy screening programs in place, most did not and there were no sites at which active outreach sought to bring members in for screening. Upon the thoughtful urging of Dr. Albert Palitz, Chair of the Chiefs of Gastroenterol-

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ogy, TPMG's Executive Director, Dr. Harry Caulfield moved to establish sigmoidoscopy screening units in every medical center in the region. Based on the case-control study finding that a 10-year screening interval was sufficient, the units were built and staffed with the goal of providing sigmoidoscopy to 10 percent of the membership aged 50 years and above each year.

The CoCaP program (Colon Cancer Prevention), [11] begun in January 1994, was the first sigmoidoscopy screening program in the country designed to serve an entire population. During its first four years, CoCaP screened approximately 60,000 members annually. A recent survey of Kaiser Permanente members found that more than 50 percent of age-eligible members now report having had a sigmoidoscopy within the past 5-10 years. This figure is much higher than levels reported nationally.

Data from the CoCaP screening examinations, along with pathology reports and follow-up colonoscopies, have been collected at DOR and entered into a large database for continued study of questions related to screening with sigmoidoscopy. Using this database, we have recently shown convincingly that neither the presence nor the size of tubular adenomas found at screening sigmoidoscopy predicts a greater likelihood of finding important adenomas in the proximal colon at follow-up colonoscopy. Rather, it is the presence of villous features in adenomas of any size that increases this risk.

We are also monitoring cancer incidence rates in the entire Kaiser Permanente membership. Given the degree of effectiveness shown in the case-control study, the CoCaP screening effort should eventually show up as a decline in the incidence of advanced colorectal cancers from the distal half of the colon and rectum. Just how long it will take to demonstrate this effect is uncertain. With complete cancer incidence data through 1996 (after three years of CoCaP), we do not yet see a significant decline in age-, sex-adjusted incidence of advanced stage cancers.

Studies of Alternative Screening Strategies (Fecal Occult Blood Testing)

Interest in colorectal cancer screening has not been confined to studies of sigmoidoscopy. Sigmoidoscopy, although effective, covers primarily the distal half of the colon and rectum, leaving approximately 40-50% of cancers undetected. Dr. James Allison, of the Division of Gastroenterology, Kaiser Foundation Hospital in Oakland, has conducted a series of important studies of an alternative screening strategy using tests for occult blood in the stool.[12,13] These studies have done much to describe the performance characteristics of fecal occult blood tests in real world settings and to propose improvements based on these characteristics.

Dr. Seymour Grossman, also of Oakland's gastroenterology division, conducted one of the first studies to compare sigmoidoscopy findings with subsequent colonoscopy findings.[14] Consistent with CoCaP data, he found that tubular adenomas, at least those of <1 cm in diameter, were not associated with increased risk for advanced proximal neoplasms at colonoscopy.

Summary

A remarkable proportion of the best research on colorectal cancer screening over the past 20 years has come from Permanente Medical Group physicians. This research has and continues to contribute to national policy in this area. It has also served to make Kaiser Permanente a leader in providing colorectal cancer screening. TPMG owes much to Dr. Gary Friedman, whose careful work produced many of the earlier contributions in this area and whose mentoring was responsible for much of what came later. ❖

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Reflections

by Gary D. Friedman, MD, MS

Summary

I am grateful to all who made possible this symposium, my rewarding career at KP, and the success of the Division of Research (DOR). In my 36-year career in epidemiology, I have seen many important developments in methodology, some of which I was slow to adopt.

One of the main reasons that KP in Northern California is one of the best settings in the world to conduct epidemiologic and health services research is our access to comprehensive, often long-term, medical records on millions of people. Although our newer computerized records are very valuable, our collection of manual charts going back over 50 years is a national treasure and must be preserved despite the storage and retrieval costs entailed. We must also guard against external threats to our access to our records for legitimate research resulting from overzealous protection of privacy. Other precious resources for research, such as the Kaiser-Orentreich frozen serum collection and tissue specimens in our pathology departments, also require care and preservation. While recognizing the value of all of our records we must be cautious about errors in data retrieved from either computer storage or medical charts.

Investigator-initiated, outside-funded research published in peer-reviewed journals must always be a primary activity of DOR. The keys to our success, both past and future, lie in our resources, objectivity, quality work completed and published, and helpfulness to others in KP.

Thanks and Acknowledgments

I feel truly honored by this symposium and thank Dr. Joe Selby, assisted by many in DOR (Diana Holt, Joey Macapinlac, Susan Mignano, Donna O'Connor, Scott Ryan, Alison Truman, Lyn Wender) and the invited speakers, all of whom made it possible. I also gratefully acknowledge all who made my career at the KP DOR so rewarding: my predecessors, Dr. Morris Collen, who persuaded me to join the department almost 30 years ago, who did so much to establish our precious data resources, and who set an example of hard work and productivity that is rarely equaled; and Dr. Ted Van Brunt, who maintained an atmosphere and fostered a culture that assured our continued success. I also appreciate the leaders of our organization who have recognized DOR's value to KP and supported us, though we have been a little "offbeat." I would mention especially, in The Permanente Medical Group, Drs. Cecil Cutting, Bruce Sams, Harry Caulfield, Jay Crosson and Philip Madvig; and on the Health Plan side, Jim Vohs, Clifford Keene, David Lawrence, Jim Lane, and the KFRI administrators, including Dick Nigro, Gil Lee, Glenda Marlow and Nancy King.

My Assistant Directors, Drs. Robert Hiatt and Joe Selby, have contributed much to the leadership of DOR, in part by covering for my inadequacies and making me look better than I was. I have been greatly stimulated by collaborating investigators in DOR and KP, of whom three of today's speakers, Arthur Klatsky, Joe Selby and Stephen Sidney are prime examples. Young investigators have also been stimulating; mentoring them and watching them grow to be independent has been one of the most satisfying aspects of my career. I have received much help from DOR biostatisticians, originally Abe Siegelaub and Hans Ury and more recently the five excellent colleagues that we now have. (It is not well known that biostatisticians are ordained clerics, empowered to pronounce one's analyses and statistical tests as kosher.) I have received indispensable computer programming by Donna Wells and Harald Kipp for many years. Similarly, I have relied on our excellent medical record analysts—most recently, Merril Jackson, May Kuwatani and Bill Frank—and superb secretarial assistance from Agnes Lewis, Stephanie Tang, Pat Crump, Lyn Wender, Susan Mignano and Mary Jeaniene Luck. DOR has had excellent administration, led by P.H. Kidd, Carolyn Quan, and Donna O'Connor. Though Donna's staff has grown along with the department, it is still lean, hardworking, and productive. Fortunately, there has been relatively little bureaucracy in DOR.

I am grateful to our outside collaborators who have brought good ideas and expertise to DOR; two of the speakers today, Julie Parsonnet and Noel Weiss are excellent examples, as is Leonard Syme here at the University of California. Finally, DOR and I owe a great deal to the overall KP organization. Although research is one of its important goals, it is not its main mission. KP has a wealth of talent that can participate in our research efforts and generally employees throughout KP have been willing to go the extra mile to help us.

Changes in Epidemiologic Methods and My Use of them During My Career

My experience as a Commissioned Officer in the U.S. Public Health Service, first at the Heart Disease Epidemiology Study, Framingham, Massachusetts 1962-1966

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GARY D. FRIEDMAN , MD, MS, is a Senior Investigator at the Division of Research, where he has worked for 30 years and was Director from 1991-1998. As a musician, he plays the oboe in two orchestras, a band, and chamber music groups. He has produced more than 250 scientific publications. (See the more detailed Biography following his article).
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(during which time I received training in epidemiology and biostatistics at the Harvard School of Public Health), then at the Heart Disease Control Program Field Station in San Francisco, 1966-1968, led me to switch my main career focus from internal medicine to epidemiology. That was a time when risk estimates from case-control studies and multivariate analysis of disease risk factors were coming into vogue in epidemiology. A major contributor to these methodological developments was Jerome Cornfield, whom I had the privilege of getting to know during both the Framingham years and my early years in DOR. One of my first papers described a comparison of the not-fully-accepted case-control vs. standard cohort analyses of risk factors for coronary heart disease in the Framingham data.[1] This methodological paper was "hot stuff" and readily published in 1966, but in retrospect, with our better understanding today, seems quite naive. In a 1968 paper from the Field Station, I believe that I and my coauthors were the first to report the well-known propensity for people with atrial fibrillation to have strokes, in quantitative terms of the relative risk, derived from a case-control study.[2] But this was given almost as an afterthought in the Discussion section, rather than as the relative risk or odds ratio given right up front in the Results, as is universally seen today.

In 1971, Art Klatsky, Abe Siegelaub, and I began a study to search for as-yet-undiscovered risk factors for myocardial infarction and sudden cardiac death. (This effort led to some important discoveries, especially the negative correlation between alcohol use and risk and the positive association of the leukocyte count and risk.)[3,4] Because I neither understood nor trusted multivariate analysis methods such as multiple logistic analysis (having had almost no exposure to them in my biostatistics training at Harvard) I developed an elaborate scheme to account for the known standard coronary risk factors. We selected our subjects from the large number who had extensive computer-stored multiphasic health checkups (MHCs) and matched cases and controls on these risk factors, made possible by the huge number of MHC examinees. Continuing my conservatism, multivariate analysis was barely mentioned in the first edition (1974) of my textbook, *Primer of Epidemiology.* Then in 1978, led by Loring Dales, we published a case-control study of diet and colon cancer in blacks.[5] Loring did introduce us to the use of multivariate analysis, in this case the method of Alvan Feinstein called prognostic stratification. Finally, I was converted, and we used logistic regression in a study of cigarette smoking and mortality[6] published in 1979 and the Cox proportional hazards model in a study of the effects of quitting smoking on mortality in 1981.[7] In 1987, the third edition of

Primer of Epidemiology had a new chapter explaining multivariate analysis methods.

The Importance of Preserving our Medical Records, A National Treasure

I have long viewed KP in Northern California as one of the best workshops in the world to do epidemiologic and health services research. An important reason is our collection of comprehensive medical records covering both inpatient and outpatient care of millions of people, often spanning long periods. KP is known for its computer-stored records, but much of DOR's research is based on abstracting manual records. Our staff now includes about 40 medical record analysts and the number has been increasing in recent years.

This collection began over 50 years ago and, obviously, many old records are no longer needed for the care of patients. The costs of storage of these records and retrieval for research are considerable and periodically questioned. Every few years I have been called upon to defend these old records from destruction and have zealously done so because I view them as a national treasure. The question has been raised again because of the merger of KP in Northern and Southern California into one division. The storage issue is especially urgent in Northern California because our long-term storage facility in Livermore will run out of space by the end of this year. KP in Southern California has more space available partly due, unfortunately, to their policy of destroying records of subscribers after they have left the Health Plan for seven years (except records of children and cancer patients).

Why I regard these records as a national treasure is well illustrated by one of the most influential studies ever done in DOR, the well-controlled study by Joe Selby and colleagues that showed that screening sigmoidoscopy prevents death from colorectal cancer.[8] Because the ascertainment of cancer cases dated from 1971 and the review of the sigmoidoscopy experience of cases and controls went back ten years before the cases' diagnoses, we needed to include records of care in the early 1960s. To my knowledge, no one ever predicted that those records would prove to be so valuable. We have looked at even earlier records in assessing the effects on children of their parents' exposures or characteristics or the effects of exposures or characteristics early in life on health and disease many years later. Lisa Herrinton is now abstracting records going back to the 1940s for her study of adolescent height and weight in relation to risk of breast cancer in our female subscribers.

There is no guarantee that our old records will prove so valuable in the future, but I think that the likeli-

hood is great. I know of no comparable medical record collection in a defined population in which long-term medical follow-up, or follow-back, is so feasible. The Mayo Clinic has a wonderful system, which goes back further—to the early 1900s,[8] but the population of Rochester, Minnesota in which the Mayo group can do population-based studies is much smaller than ours and lacks the tremendous ethnic and socioeconomic diversity of our subscribers.

I have been meeting with persons in charge of medical record storage in KP's California Division, and they understand how important our records are, especially in view of KP's increasing promotion of research as a way to demonstrate its leadership in providing health care. We have been exploring ways to lower the cost of storing the little-used, older records and to support their preservation and retrieval through research-funding mechanisms.

External Threats to Research Using our Medical Records

There are external as well as internal threats to our access to medical records. With the growth of computer data banks of all sorts, the public is understandably concerned with the possibility of invasions of privacy—in the medical area, for example, with clerks at insurance companies seeing their medical records. This has led to proposals for sweeping privacy legislation that along with preventing abuses, would prevent researchers from looking at medical records without specific permission, not obtainable after a patient has died. As illustrated by the sigmoidoscopy study mentioned above, studying records of the deceased is essential if we are to find ways to prevent premature death.

Fortunately, recent proposals for legislation in California and at the federal level have been more reasonable, protecting confidentiality but allowing legitimate medical and public health research to go forward under the watchful eyes of Institutional Review Boards.

Other Priceless Resources

Besides medical records, the resources of our superb epidemiologic workshop include the 250,000-specimen frozen serum bank, now at the Orentreich Foundation for the Advancement of Science in New York, and the tissue specimens collected by our pathologists. We must guard against the loss, destruction, and inappropriate use of these biological specimens and be very careful to assure the complete and timely return of tissue to our pathology departments so that our pathologists will continue to assist us. The value of the serum bank has been well shown in several investigations, perhaps best exemplified by the

studies in which Dr. Julie Parsonnet discovered that *Helicobacter pylori* infection predisposes to cancer of the stomach, both adenocarcinoma[9] and lymphoma.[10]

Some Cautions About our Valuable Computer-stored Records

Our computer-stored records are also a tremendous resource, mainly because information in them is so much more accessible than that in manual records. We have comprehensive hospital diagnoses stored since 1971 and outpatient diagnoses and pharmacy records since 1994, as well as records from pathology, laboratory tests, and imaging procedures. It should be noted that the computer recording of outpatient diagnoses and of prescriptions dispensed from the pharmacy was well developed and operating in KP's San Francisco facility in the late 1960s under the leadership of Drs. Collen and Van Brunt. The recently implemented Outpatient Summary Clinical Record (OSCR) and Pharmacy Information Management System (PIMS) have improved on the early clinic diagnosis and pharmacy systems but, in many ways, were "reinventing the wheel."

I urge my colleagues to make good use of our computer-stored records. At the same time, recognize their limitations and maintain a healthy skepticism about what you find in them. Usually, a more full story can be found in the chart. In a postmarketing study of the antibiotic, clindamycin,[11] we found two cases of diarrhea during three months of follow-up in the computer records. In the manual charts, we found ten. There were probably several reasons for the discrepancy, one of the most important being that the drug was prescribed frequently by otolaryngologists and there was no provision on their clinic diagnosis form for them to easily record the occurrence of diarrhea in their patients. In a study of the possible carcinogenic effects of lindane,[12] applied topically for scabies or pediculosis, four of the skin cancer diagnoses turned out to be Kaposi's sarcoma in AIDS patients, which was not apparent in the computer records. Lifestyle factors could readily connect these infestations with AIDS. Another apparent lindane user who developed breast cancer had used her KP identification card to obtain the prescription for her husband. These errors were sufficient to reduce the apparent excess risk of cancer among lindane users to statistical insignificance.

So be careful. If you cannot review all the manual records of study subjects, at least review the critical ones or a random sample of all of the records for validation.

Chart Review is Subject to Error, Too.

I find it very difficult to review charts and am glad that we have so many capable medical record ana-

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lysts in DOR. No matter how good analysts are, some errors in abstraction are inevitable. So a study involving chart review needs some rereading of charts to measure the error rate and to find out what errors are apt to occur, for training and quality improvement. Two excellent, experienced medical record analysts abstracted the data for our case-control study of bladder cancer screening by urinalysis.[13] Initially and under supervision, both of them abstracted the same records for training. Then, one and six months after starting their independent work, both abstracted the same five charts to measure accuracy. In the one-month test there were 32 errors in 924 data items, or a 3.5% error rate. At six months, there were 40 errors in 1008 data items, yielding a 4.0% error rate. This is the magnitude of error one should expect from competent chart abstractors.

Be Especially Careful of Rare Findings or Events, Whatever the Data Source

I became acutely aware of the inaccuracy of rare occurrences in data when we became heavily involved in research on twins. Simple calculations showed that when twins were discordant for a characteristic, eg, one smoked cigarettes and the other did not as reported on a questionnaire, these apparently discordant pairs probably contained a substantial fraction of truly concordant pairs because of errors in the data. Twins are infrequently discordant for many characteristics, and the dilution by truly concordant twins becomes worse as discordance becomes less frequent. In describing this problem, I proposed that this partially explained why smoking-discordant twins seemed to differ less in disease occurrence than would be expected, given the known effects of smoking on health.[14]

My experience in searching for patients with rare diseases or findings in various data bases has confirmed this concern about accuracy. When you find only a few such patients, check their records carefully. You will often discover that about half are people with other conditions that have been miscoded.

Investigator-initiated Research in our Setting

Wouldn't it be nice if DOR were totally supported internally and we were all on "hard" instead of "soft" money? Realistically, for this to occur we would have to devote all of our energies to responding to the needs of our management and to answering their pressing questions. If we did this well, our livelihoods would be secure and we would not have to worry about competing for grants or establishing good publication records to demonstrate productivity to peer reviewers. This might also be tempting to our parent organization; we would direct all of our energies to serve KP's immediate needs as perceived by management in return for hard-money support.

Such a change would be most unfortunate,[15] as is well illustrated by Joe Selby's study of sigmoidoscopy.[16] Previously, Joe had helped us on the U.S. Preventive Services Task Force (USPTF) to review the literature on whether screening by sigmoidoscopy prevents death from colorectal cancer. He and I concluded[17] that there were no good, well-controlled studies that demonstrated the efficacy of this procedure, even though it was being recommended by prestigious authoritative bodies such as the American Cancer Society. The Task Force agreed, and its recommendation concerning the clinical application of screening sigmoidoscopy was neutral.[18] Clearly, this procedure could detect cancer early and lead to the removal of premalignant polyps; but since it was unpleasant and costly, more evidence concerning its efficacy was needed.

Joe recognized that KP was an excellent setting for a case-control study of this question. Our records could reveal who died of colorectal cancer—the case subjects, and screening sigmoidoscopy had been offered at some of our medical centers and recorded in our records. He designed a case-control study in which the case subjects were compared with control subjects, the main focus being on their experience of sigmoidoscopy in the ten years before the cases' diagnoses. Motivated by his personal interest and recognition of the need for such a study, Joe applied for a National Cancer Institute (NCI) grant. Peer review led to the application initially being turned down because Joe and I had not considered a methodologic problem known as healthy-screenee bias. We consulted with Noel Weiss, a leading expert in case-control studies of screening tests. As a result, an improved study design was resubmitted, and the study was approved and funded by NCI.

The study was completed and showed elegantly that screening sigmoidoscopies do prevent death from colorectal cancers within their reach. After additional peer review, the study was published in the prestigious *New England Journal of Medicine*[16] and received considerable attention both nationally and within KP. Confirmed in a smaller investigation elsewhere,[19] our findings led the USPTF to change its recommendation regarding screening sigmoidoscopy from neutral to favorable.[20] The KP gastroenterologists were also impressed, and a systematic screening program for our subscribers,

known as Colorectal Cancer Prevention or CoCaP, was implemented.

This study was investigator-initiated, outside-funded, and published. What would have happened if DOR had been totally devoted to directed in-house research (assuming that someone of Joe Selby's caliber would have been willing to work under such an arrangement)? First, the grant application was submitted in 1987, and the study was conducted from 1988 to 1991 at a cost of $457,000. I sincerely doubt that management at that time would have viewed this question of sufficient concern to devote almost a half million dollars to it. Second, with total internal support, we would probably not have benefited from external peer review of the study design, and the methodologic flaw would not have been detected. If anyone in KP had been aware of healthy-screenee bias, it should have been Joe and I, and we were not. Finally, if the study had not been published in a respected peer-reviewed journal, the findings would have been less impressive to our physicians and managers. If our leadership had instituted the CoCaP program on the basis of a purely internal unpublished study, it would probably have been met with skepticism and resistance, given the extra work, costs, and difficulties involved.

This example clearly shows several advantages of peer-reviewed published research and why it should always be a big part of our mission. This does not mean that DOR should become an ivory tower lacking organizational concerns. We must respect and respond to the interests and needs of KP. Not only would we not exist without its support, but we in DOR believe in KP, its principles and its social mission. We want to contribute to KP's success in providing high quality care to its subscribers. Just as our work benefits the organization, the interaction with KP leaders and clinicians stimulates us to identify and investigate interesting questions.

The Keys to DOR's Success, Past and Future

I think we have been very successful in using our rich research resources. DOR is internationally known in epidemiology and health services research and we are increasingly valued by KP. We achieved this success not by taking people out to lunch and schmoozing them, as some worried members of DOR have urged me to do. We achieved this success not just by starting projects but by finishing and publishing them, and by making sure that we maintain our objectivity. We achieved this success by being helpful whenever we can to our colleagues in KP.

The keys to DOR's success, both past and future, are listed.
1. Resources
2. Objectivity
3. Quality work
4. Completion and publication
5. Helpfulness ❖

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"We in DOR believe in KP, its principles and its social mission."

"Just as our work benefits the organization, the interaction with KP leaders and clinicians stimulates us to identify and investigate interesting questions."

Gary D. Friedman, MD, MS: A Biography
by Arthur L. Klatsky, MD

Gary Friedman is an internationally known, outstanding physician-epidemiologist who has been with the Kaiser Permanente Medical Care Program (KPMCP) since 1968. Born in Cleveland, Ohio on March 8, 1934, he attended Antioch College and the University of Chicago (BS 1956) and received his MD at the University of Chicago in 1959. His internship and residency were served at the Harvard Medical Services, Boston City Hospital and at University Hospitals in Cleveland, Ohio. This was followed by obtaining an MS degree (biostatistics) from the Harvard School of Public Health in 1965 and American Board of Internal Medicine certification. He worked with the Framingham Heart Study (1962-66) and as Chief of the Epidemiology Unit, Heart Disease Control Program, U.S.P.H.S. in San Francisco before joining the KPMCP. At the KPMCP Division of Research (DOR), he served as Senior Epidemiologist (1968-76), Assistant Director (1976-91), Director (1991-98), and is now Senior Investigator.

Gary is substantially responsible for developing one of the first and largest epidemiological research programs in an HMO. His prodigious output of work has been in diverse areas of epidemiology, including cancer, cardiovascular disease, gallbladder disease, adverse drug reactions, twin research, effects of smoking and alcohol, and evaluation of screening tests. His textbook, *Primer of Epidemiology,* now in its Fourth Edition, is widely used by medical schools and health professionals (>80,000 copies sold) and has been translated into Spanish, Italian, and Chinese. He has authored more than 250 scientific papers or book chapters. He is one of the few epidemiologists to win a coveted seven-year, $4-million Outstanding Investigator Grant from the National Cancer Institute (1989-96; renewed from 1994-2001).

Among Gary's epidemiologic "firsts" are the following:

- First to quantitate the risk of stroke in relation to atrial fibrillation (*Circulation* 1968; 38: 533-41).
- First to show the relationship of cigarette sale differences in U.S. states to risk of myocardial infarction (*J Chron Dis* 1967; 20: 769-79).
- First community-based study of risk traits for cholelithiasis (*J Chron Dis* 1966; 19: 273-92).
- First to report that the leukocyte count is an independent predictor of myocardial infarction (*N Engl J Med* 1974; 290: 1275-8), sudden death (*Circulation* 1975; 51-2, Suppl.III: 164-9), and hypertension (*Prev Med* 1988; 17: 387-402).
- First to conduct a large-scale survey of drugs to discern relationships to cancer (6 articles), resulting in a MERIT grant award from the National Cancer Institute.
- First to develop a twin research program in an HMO (5 articles).

His academic affiliations are:

Lecturer, University of California San Francisco and University of California Berkeley; Consulting Professor, Department of Health Research and Policy at Stanford University. Gary has been on the Editorial Boards of *The American Journal of Epidemiology, HMO Practice,* and the *Journal of Medical Screening.* Other community involvement includes or has included service on: Epidemiology and Disease Control Study Section, National Institutes of Health; U.S.-U.S.S.R. Working Group on Sudden Cardiac Death; U.S. Preventive Services Task Force; Scientific Review Panel on Toxic Air Contaminants, California Air Resources Board; Advisory Committee, Merck Foundation/Society for Epidemiological Research; and Senior Advisor, Expert Panel on Preventive Services. He is a member of numerous professional societies. He is President-Elect of the American Epidemiologic Society and on the Executive Committee of the Society for Epidemiological Research.

Gary is a devoted husband (married Ruth Schleien on 06/22/58), father (Emily, Justin, and Rick), and grandfather (Sophie and Nathaniel). His diverse interests include music and hiking. He has been a regular runner since age 27 and now runs 15-20 miles per week (bicycles regularly another day). Gifted with perfect pitch, he has played the piano since childhood and took up the oboe at age 54. He has played the oboe in numerous chamber music groups (was on Board of Directors, Chamber Musicians of Northern California) and is a performing member of the San Francisco Civic Symphony, the University of California San Francisco Orchestra, and the Bohemian Club Band.

Selected Publications By Gary D. Friedman, MD, MS (of over 260)

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