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BIOBEHAVIORAL RISK FACTORS

Reflections on Present and Future Research on Bio-Behavioral Risk Factors

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There is a wealth of data linking behavioral and social factors to health outcomes, and these data have led to real advances in our understanding of the bio-behavioral basis of many health conditions, both physical and mental. That's the good news. The bad news is that we have a plethora of risk factors. Lack of integration among these factors has left the public confused as to the relevance and importance of the information available.

Further progress will depend on some fundamental changes in the way in which we conceptualize and investigate this area. This may be particularly true as we try to integrate knowledge of behavioral, social, psychological and socio-environmental factors in our understanding of the natural history of physical and mental health.

Table 1 presents a partial list of behavioral and psychosocial risk factors, very broadly construed, which have been shown to be related to a variety of health outcomes. This list could be three times as long. For example, when Jenkins (1976) reviewed the evidence, a number of years ago, for the role of psychosocial factors in cardiovascular disease he referenced several hundred articles. If the same review were to be carried out today, the number would be, I imagine, an order of magnitude larger.

One can ask what the advances have been—there have been many—I will illustrate a few from the cardiovascular area. Some of the highlights will come from work in my laboratory and some from the work of others.

Some of the most interesting work in this area comes from the team of investigators at the University of Pittsburgh and the Bowman Gray School of Medicine (Manuck *et al.*, 1988). Their research with a non-human primate model has led to a series of exciting findings showing that sympathetic activation in response to a social stress leads to increased atherosclerosis (Figure 1). In this figure, you can see the extent of coronary atherosclerosis for monkeys raised in both stable and socially unstable conditions for both dominant and non-dominant

Table 1

Partial List of Behavioral and Psychosocial Risk Factors

Smoking	Anger expression/
Physical Activity	Control
Relative Weight	Cynical Distrust
Diet	Control
Alcohol	Stress
Coffee	Sense of Coherence
Antioxidents	Neuroticism
Fat	Hardiness
Social Class	Perceived Health
Social	Optimism
Support/Networks	John Henryism
Life Satisfaction	Job Strain
Depression	Status Incongruity
Type A Behavior	Self-referent Speech
Pattern	Personal Uncertainty
Hostility	Daily Hassles

monkeys. There is a substantial impact of the socially unstable condition on coronary atherosclerosis for the dominant monkeys. Dietary factors were held constant, in this case a mildly atherogenic diet for both experimental and control animals.

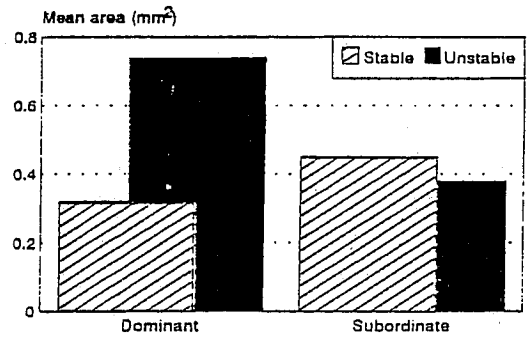
One of the most exciting results to come from this work is that treating the dominant monkeys with propranolol removes the effect of the unstable environment on the dominant animals (Kaplan *et al.*, 1987). This is a very elegant way to provide data which supports a role for sympathetically driven vascular reactivity in the face of social disruption as being important in the pathogenesis of coronary heart disease.

The development of non-invasive imaging techniques is beginning to revolutionize out ability to understand some of the pathways which link behavioral and social events to health outcomes. Figure 2 shows an example

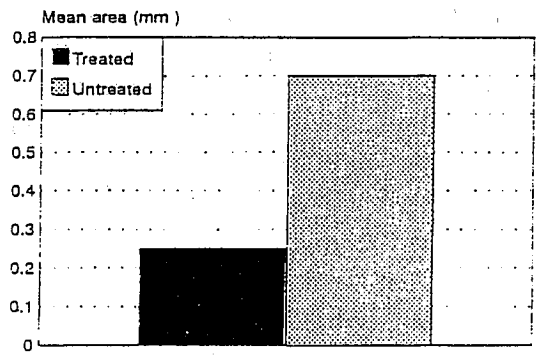
Figure 1

Extent of coronary atherosclerosis by environmental and individual characteristics, and Alteration of effect of social disruption in dominant cynomolgus monkeys by propranolol

(adapted ref. 2 & 3)



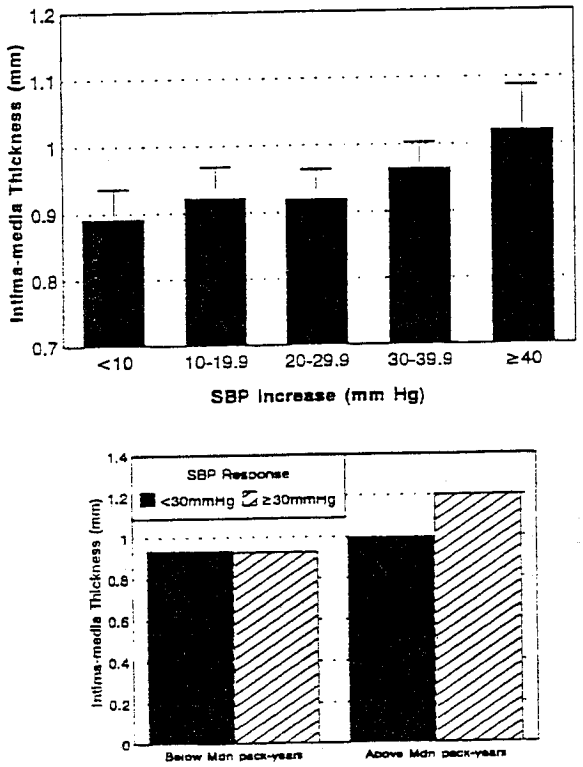
Kaplan, Manuck, Clarkson et al. (1982)



Kaplan, Manuck, Adams et al. (1987)

Figure 2

Extent of carotid atherosclerosis by anticipatory systolic blood pressure response, and Carotid atherosclerosis by anticipatory blood pressure response and smoking

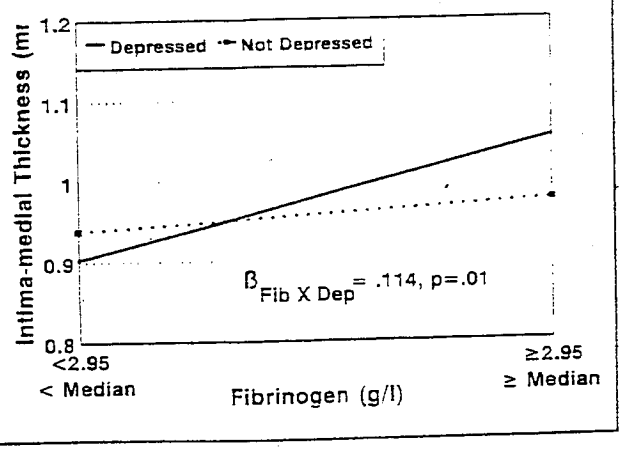


of the use of one such technique from my laboratory. The figure shows the association between systolic blood pressure response to an anticipatory stress—the difference between a resting systolic blood pressure taken during a standard blood pressure protocol and the same sitting, resting pressure taken just before the beginning of a maximal exercise—and the extent of carotid atherosclerosis determined by B-mode ultrasound. As you can see there is a regular and linear relationship between the anticipatory response and the extent of carotid atherosclerosis. This research, taken from a study which we are conducting in eastern Finland again suggests a role for sympathetically driven vascular reactivity in the development of atherosclerotic vascular disease. The figure also shows the results when we took this systolic blood pressure response and looked at its association with carotid findings as a function of smoking. The association was found only in heavier smokers—so we see a bio-behavioral interaction, with the anticipatory stress response seeming to only be associated with carotid findings in heavy smokers.

Similar kinds of bio-behavioral interactions were shown in another study from this cohort in which we examined the association of fibrinogen levels with carotid atherosclerosis (Figure 3). In the analyses shown here, we found that the association between fibrinogen and atherosclerosis varied as a function of depression measured by the MMPI. Depression seemed to potentiate the impact of fibrinogen on atherosclerosis. These studies indicate that psychosocial factors may play a very important role in the development of atherosclerotic heart disease.

Figure 3

Carotid atherosclerosis by fibrinogen and depressive status

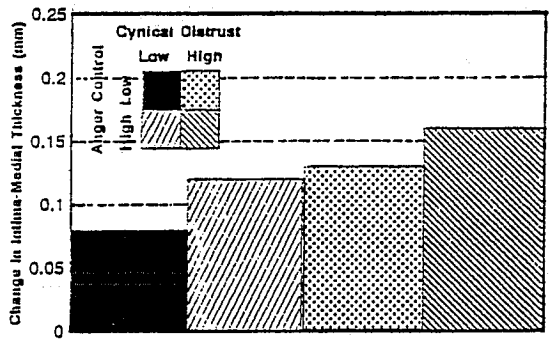


Another factor which has received considerable attention is that of hostility. Figure 4, from the same study in eastern Finland, illustrates the importance of a factor related to hostility, cynical distrust, in the two year progression of carotid atherosclerosis. The figure shows the amount of change in carotid atherosclerosis as a function of cynical distrust and anger control, adjusted for baseline level of atherosclerosis and lipids, smoking, blood pressure and a variety of other factors. As you can see, those who were highest on cynical distrust and anger control had the greatest progression of atherosclerosis.

Figure 4

2-year progression of carotid atherosclerosis by cynical distrust and anger control

(adapted from Julkunen et al, in press)



Julkunen, Salonen, Kaplan et al. (1993)

These are only illustrations of a vital and growing area of bio-behavioral research. We are getting more and more knowledge about some of the biological pathways which mediate psychosocial and bio-behavioral effects, in this case on cardiovascular disease. There are many important and substantial exciting contributions coming from this area.

Having discussed some of the more successful findings, let us consider six areas in terms of future directions. The first is to take social class seriously. The second is the study of the natural history of risk factors. The third is to abandon the notion of independence. The fourth is to consider the ecologic niches in which people live. To probe diversity is the fifth. And the last, to examine the public health implications of bio-behavioral research. Now that these are stated very telegraphically let me go through them one at a time.

I. Take social class seriously

The association between various measures of social class and a wide variety of health outcomes has been known for hundreds of years. Anyone who has looked at this field cannot help being impressed by the stability of these associations across time, across measures of social class and across geographic place (Haan *et al.*, 1989).

In fact it is so widespread that the way we deal with it is to control for it, adjust for it, pretend it's not there, or take out its impact in some other way. I would like to propose that we need to do just the opposite, to probe social class differentials in health much more extensively and to really see this as an important source of heterogeneity in the health experience of populations and one which is desperately in need of explanation.

For example, Figure 5 shows the fatality rates for women on the Titanic as a function of a proxy for social class—ticket class. Although it was women and children first, not all women were first—the lowest mortality rates were among the first class women and the highest among those in third class. Figure 6, from a

Figure 5

Fatality rates for women on the Titanic
(adapted from Lord, 1955)

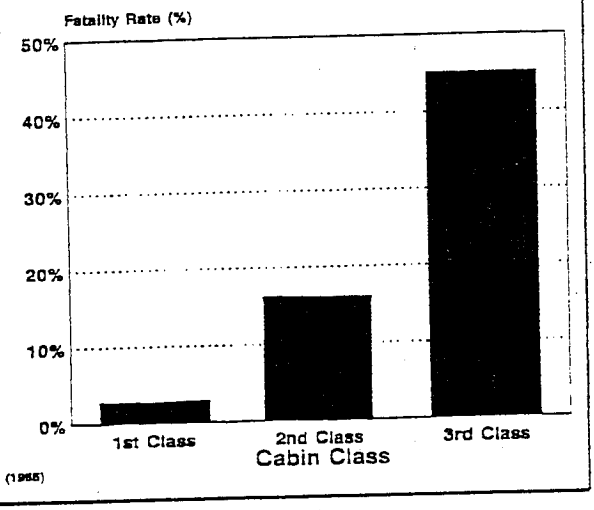
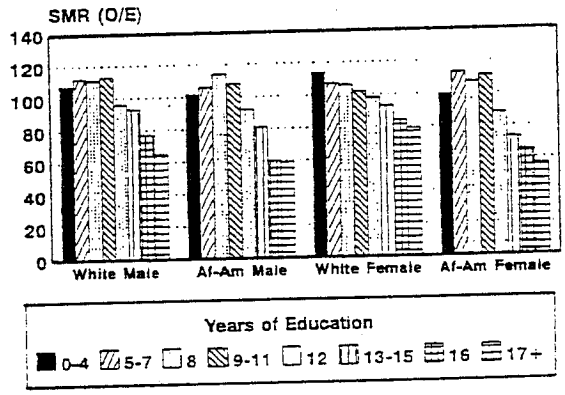


Figure 6

All-cause mortality by education level, National Longitudinal Mortality Study (adapted from Rogot et al., 1992)



study of over a million people in the United States, shows the association between all cause mortality and educational level. Generally speaking, people at the higher educational levels do the best and people at the lower levels of education do the worst. For those who remain alive the prevalence of fair or poor health by education from the National Health Interview Survey shows a linear relationship (Figure 6). From the same survey, there is a large list of health conditions which are more prevalent in those with less than a high school education (Table 2).

Survival also appears worse among lower social class patients. In this case (Figure 8), patients with documented coronary artery disease showed a monotonic increase in survival rates as a function of income even after extensive adjustment for prognostic indicators.

Quality of life is also related to socioeconomic factors. A recent study by Guralnik *et al.* (1993) examined active life expectancy as a function of education level. The growing interest in active life expectancy is based on the observation that we want to "add life to years, not just years to life." These investigators found that those who had greater levels of education had greater active life expectancy (Figure 9). So if you survive to 65 years or beyond, your future quality of life will be heavily dependent on your current socioeconomic level. We are currently examining how this applies to domains beyond physical functioning in a 29-year followup of the Alameda County Study, a population-based study of approximately 7,000 people in Alameda County, CA.

Turning to mental health measures, there are also strong gradients associated with social class. Figure 10 shows nine year incidence of high levels of depressive symptoms as a function of education and income from the Alameda County Study. There is increasing incidence of high levels of depressive symptoms associated with low education and with low income.

Table 2

Chronic Conditions More Prevalent Among Those With <12 Years of Education

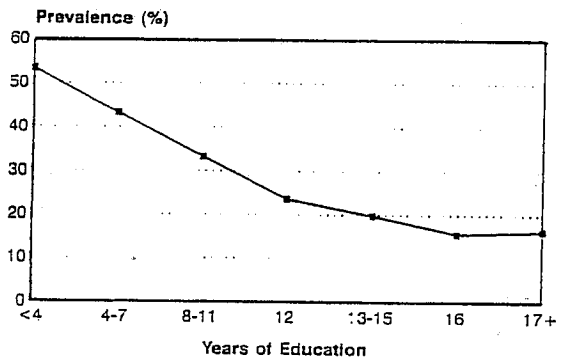
National Health Interview Survey, 1989: 65+ years

Arthritis	Goiter
Gout	Diabetes
Intervertebral disc dis.	Anemias
Bunions	Migraine
Psoriasis	Neuralgia/Neuritis
Visual impairment	Ischemic Heart
Cataracts	Disease
Hearing Impairment	Other Heart Disease
Speech Impairment	Hypertension
Paralysis	Cerebrovascular
Ulcer	Disease
Abdominal hernia	Hardening of the
Gastritis	Arteries
Kidney disease	Varicose Veins
Indigestion	Hay Fever
Diverticulitis	Chronic Sinusitis
Constipation	Emphysema

Figure 7

Prevalence with fair or poor health by education, National Health Interview Survey

(adapted from Series 10, No. 179)

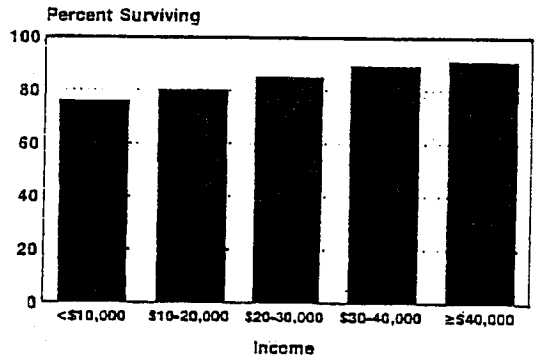


Series 10, No. 179

Figure 8

5-year survival of patients with coronary artery disease by income

(adapted from Williams et al., 1992)

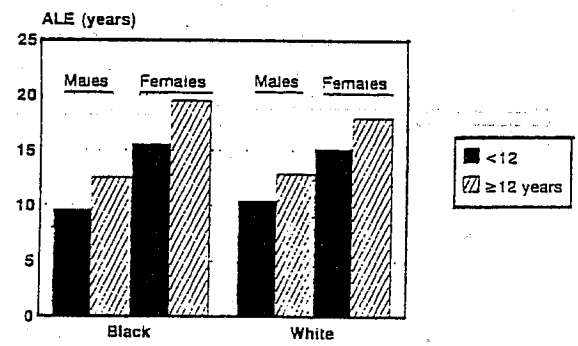


Williams, et al. (1992)

Figure 9

Active life expectancy at age 65 by education and race

(adapted from Guralnik et al., 1993)



Guralnik et al. (1993)

Similar relationships apply to many behavioral risk factors. Again from the Alameda County studies, Figure 11 shows that quitting smoking was related to income with those at the highest income showing the highest rates of quitting and those at the lowest income showing the lowest rates of quitting. In general, the adoption, maintenance and elimination of most high risk behaviors are related in the same way to socioeconomic factors.

In fact, most behavioral, psychosocial, and socioenvironmental risk factors are related to socioeconomic level. In another study in Alameda County, this done in 1989-1991, not only were behavioral risk factors, health conditions and preventive behaviors related to to income level, but also living in an unsafe neighborhood, being a crime victim having less than two close friends, having no sources of tangible support, no sources of emotional support, no health coverage, no money to see a physician, no job control and feeling unappreciated.

For those interested in hostility and anger issues, the next figure (Figure 12) shows levels of cynical distrust, from a study we are conducting in eastern Finland, as a function of education, income or childhood socioeconomic conditions before age 10. The most cynically distrustful people are those who have the lowest education, the lowest income or the lowest childhood economic circumstances. This certainly suggests a strong environmental component for cynical distrust.

In attempting to understand these complex relationships the usual procedure is to statistically adjust, using some type of regression procedure, for a variety of behavioral and social risk factors to see if we can explain away the association. Figure 13 illustrates this approach with a measure of ischemia resulting from exercise obtained from a population sample in Eastern Finland. Those who are in the lowest income quintile had roughly twice the risk of showing an ischemic response to exercise. We then adjusted for a long list of behavioral risk

Figure 10

Incidence of high levels of depressive symptoms by education and income

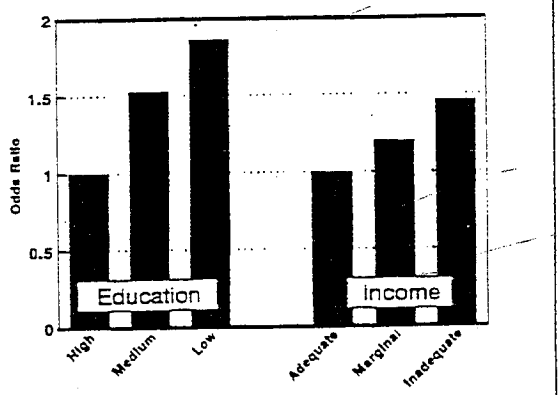


Figure 11

Smoking cessation by income

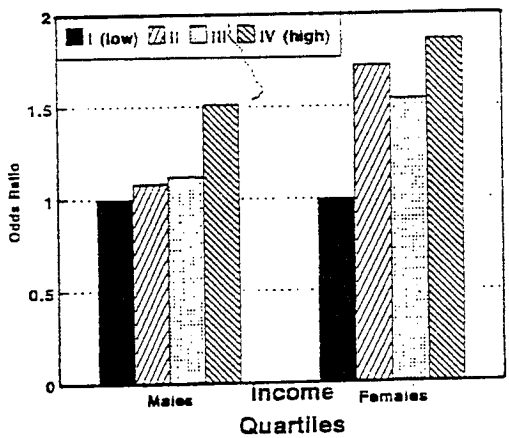


Figure 12

Cynical distrust by education, income, and childhood socioeconomic status

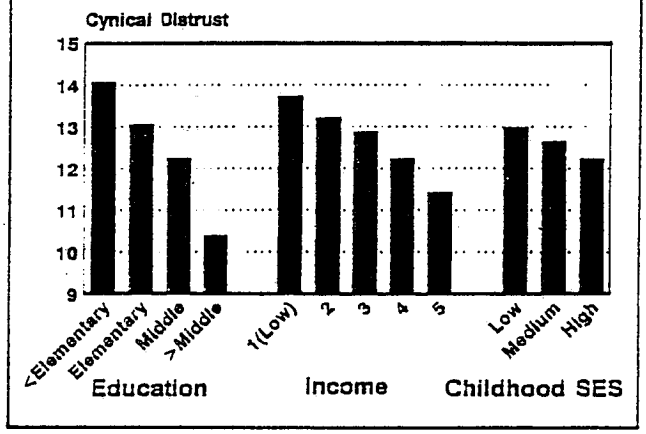
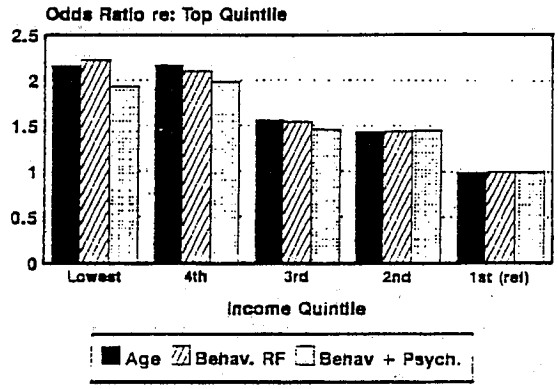


Figure 13

Ischemia on exercise by income with adjustment for age, behavioral, and psychosocial factors



factors: smoking, lipids, alcohol, relative weight, physical activity, and fibrinogen. Adjustment for these factors really made little difference in the income/ischemia on exercise association.

A number of psychosocial variables were then added to the analysis: cynical distrust, Jenkins Activity Survey Type A score, Framingham Type A score, MMPI depression, Sense of Coherence, John Henryism, and measures of job strain. The results indicated that these variables also did not influence this association. This is a recurrent pattern—when we see associations between socioeconomic factors and health outcomes, it is the rule rather than the exception that adjustment for other possible explanatory variables does not influence the results.

In addition to the social policy implication of socioeconomic gradients, and the changes in those gradients over time, we need to see socioeconomic gradients in health as an opportunity to understand much more about the natural history of health status, and to use this knowledge to inform our understanding of the bio-behavioral links with health over the life span.

II. Study Natural History

It is common in bio-behavioral research, whether it be done in the context of behavioral medicine, epidemiology, psychosomatic medicine, health psychology, or other disciplines, to give scant attention to the natural history of risk factors, their introduction, progression, and disappearance over time. However, there is much to be learned, both substantively and methodologically, from the natural history of bio-behavioral risk factors.

For example, Figure 14 from the Alameda County Study shows changes in levels of leisure-time physical activity as a function of smoking, level of depressive symptoms, and social isolation (Kaplan *et al.*, 1991). As you can see, all of these factors were associated

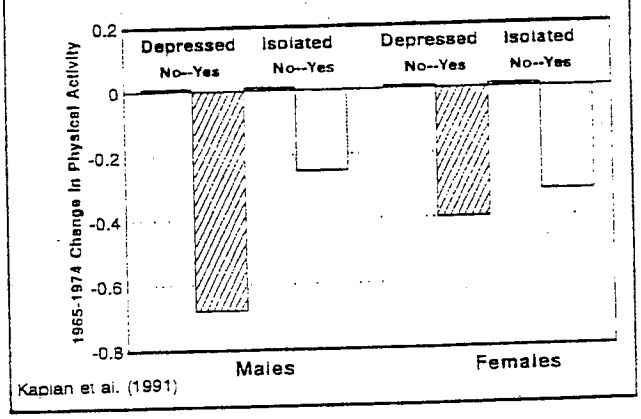
with 9-year declines in physical activity. The next Figure (Figure 15) illustrates the role of depression and physical activity in the incidence of social isolation. As you can see, low levels of leisure-time physical activity and high levels of depressive symptoms are both strongly associated with increased incidence of social isolation. Similarly, social isolation and physical activity are related to the incidence of depression so that those who were socially isolated or who were sedentary tend over time to report much higher rates of high levels of depressive systems (Kaplan *et al.*, 1987) (Figure 16). Figure 17 verifies these observations in that those who were physically active at two points in time separated by nine years subsequently have the lowest levels of depressive symptoms, and those who were inactive at both times had the highest level (Camacho *et al.*, 1991). In addition, the Figure shows that changes in physical activity were also associated with the subsequent natural history of depressive symptoms.

Temporal factors are important in understanding the natural history of risk factors. For example, Figure 18 displays the association between childhood socioeconomic conditions (Kaplan & Salonen, 1990) and adult risk factors. Those who were poor as children had higher total cholesterol, lower physical activity, higher LDL, lower HDL, and were more likely to be smokers. Thus, longitudinal studies beginning in childhood are necessary to truly understand the natural history of risk factors.

Changes in smoking consumption in the United States are a good illustration that many of the important changes in risk factors levels in the population are not driven by individual decision making, but reflect large-scale social events (DHHS, 1989) (Figure 19). Many behavioral factors related to health outcomes are strongly driven by societal forces not under the control of individuals; behavioral medicine must consider larger units of analysis than the individual, i.e., changes in social norms and socioenvironmental events.

Figure 14

Change in physical activity by depression and social isolation



Kaplan et al. (1991)

Figure 15

Incidence of social isolation by physical activity and depression

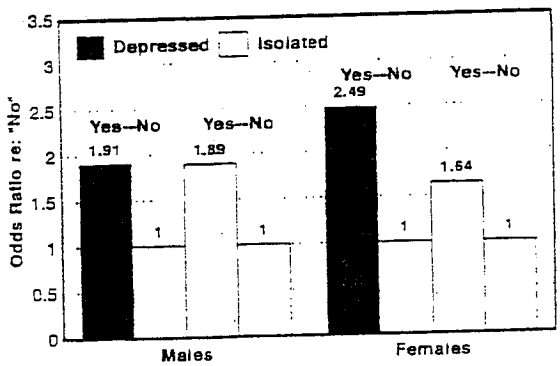


Figure 16

Incidence of depression by social isolation and physical activity

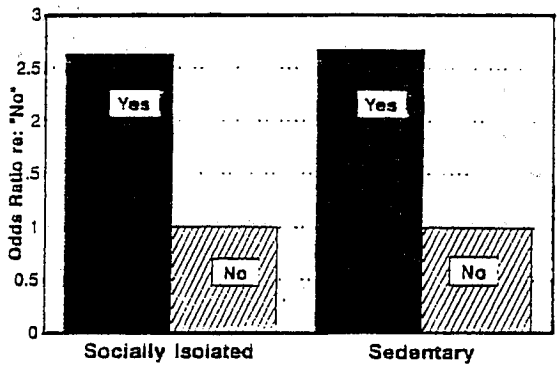


Figure 17

Incidence of depression by 9-year change in physical activity

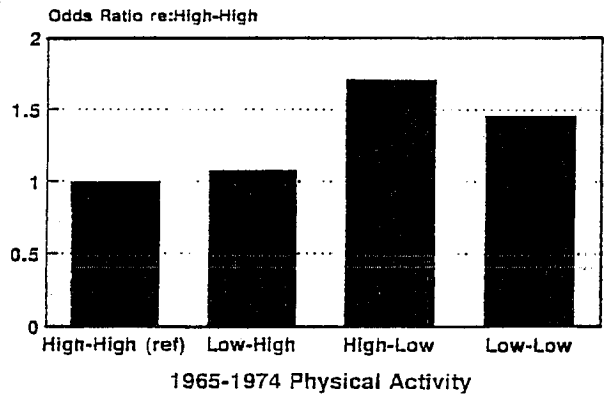


Figure 18

Childhood socioeconomic conditions and adult risk factors

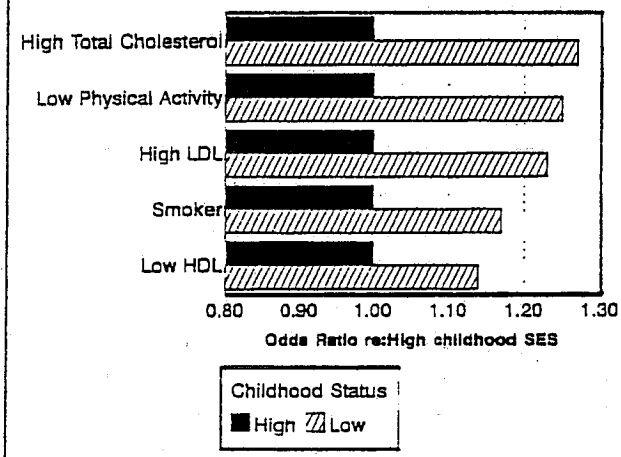
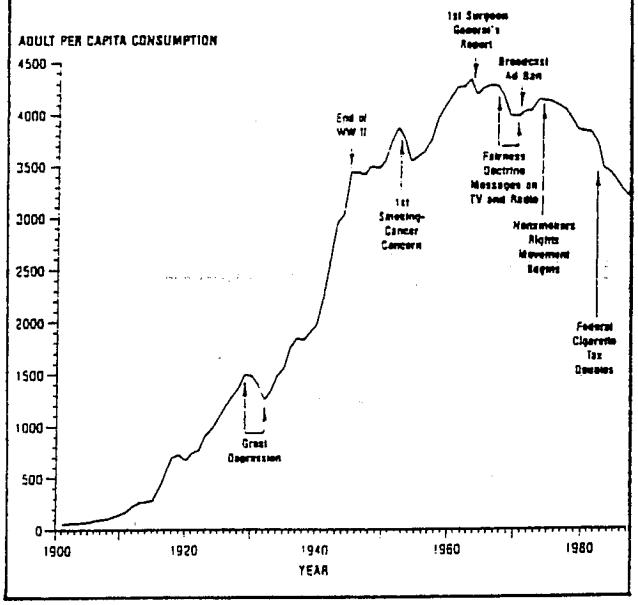


Figure 19

Cigarette consumption trends



III. Abandon the Notion of Independence

As mentioned earlier, there are methodologic issues to be addressed in understanding the relationship of biobehavioral factors to health outcomes. In the previous section on the natural history of risk factors, you may recall that everything was associated with everything—that is, level of depressive symptoms predicted changes in physical activity and incidence of social isolation; social isolation predicted changes in physical activity and incidence of high levels of depressive symptoms; and, level of physical activity predicted incidence of social isolation and high levels of depressive symptoms.

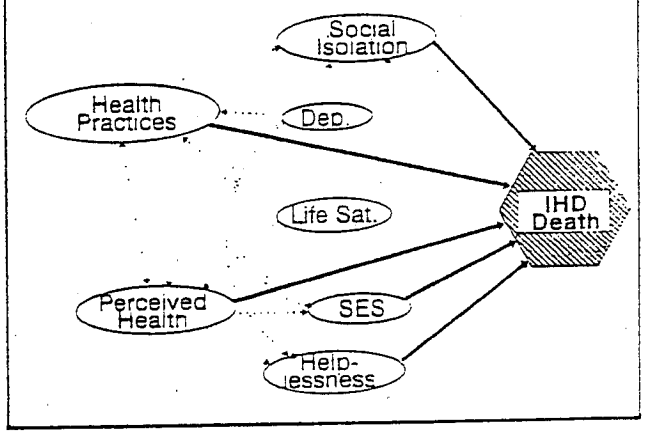
We need to start thinking seriously about our standard approach to analysis involving multivariate analyses which evaluate the "independent" effects of one factor on another. The standard approach is to put a series of potentially important factors into a multivariate model, let them compete in terms of effect sizes and variability, and finally come up the "independent" factor.

This focus on single independent risk factors leads to research which competes as to which bio-behavioral risk factor is the most important. Unfortunately, this distorts the complexity of the systems we are studying, and does a disservice to the complexity of the bio-behavioral determination of health status. Rather than trying to reduce everything to a single factor or pathway, we should be looking at patterns of associations, clustering of factors over space and time, and complexity in biological pathways.

Another example from the Alameda County Study (Figure 20) summarizes the results of analyses of how well behavioral and social risk factors predicted the risk of death from ischemic heart disease. The solid lines show "independent" effects and the dotted lines show indirect pathways (Kaplan, 1985). If all of these factors were entered into a multivariate model, the results would focus only on the "independent" effects; the pattern of interconnections between all these variables and the system of relationships are, in fact, of greatest interest. This tendency to place multiple variables into a regression model does tremendous disservice to the dense recursive and reciprocal relationships between the factors we are studying.

Figure 20

Behavioral and psychosocial pathways and risk of death from ischemic heart disease-I



The cross sectional measurement of risk factors, even in a longitudinal study, is uninformative with respect to the casual ordering between variables. That is, when we do this kind of analysis in which all factors are measured at the same time we potentially lose the fact that one risk factor may be importantly involved in the development of the another risk factor.

When some of these temporal processes (Figure 21) are considered, the analyses become admittedly more complex, but it may be a much more realistic representation of the complexity of what we are studying. Also, cross-sectional measurements of variables and the typical "multivariate stew," may give us what are statistically independent estimates of risk factor effects, but this concept of statistical independence may bear little relationship to the real world. Risk factors cluster together cross-sectionally and over time, and the recursive and dynamic relationships between them, which may be of critical biologic importance, are not captured by the usual analyses. The simple cause-effect model of relationships characteristic of traditional physics simply does not hold for human behavior, nor for the complex bio-behavioral pathways which are the determinants of health status in individuals and in populations.

IV. Consider the Ecologic Niche

To address the problems noted above will require more than new models, however interesting and useful that may be. We must change our focus to consider the spatial and temporal clustering of risk factors and to view patterns of risk factors over time and in space, i.e., geographically, as the object of our analysis.

For example, a number of years ago we examined the association between residence in a poverty area and risk of death (Haan *et al.*, 1987). Figure 22 shows the probability of surviving without a death from ischemic heart disease for those residents of the Alameda County study who lived in a poverty area versus those who did not live in such a poverty area. We found, not surprisingly, substantially better survival among those who lived in the non-poverty area. What was surprising was

Figure 21

Behavioral and psychosocial pathways and risk of death from ischemic heart disease-II

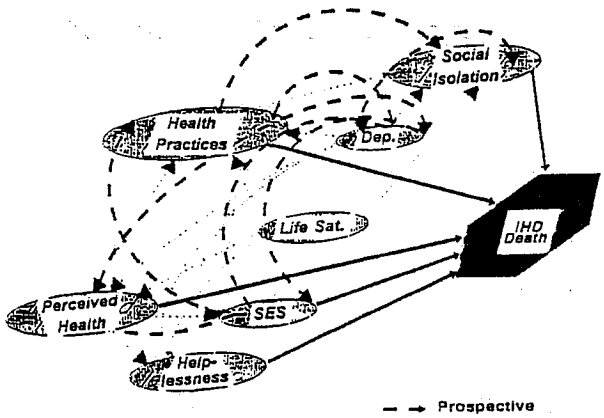
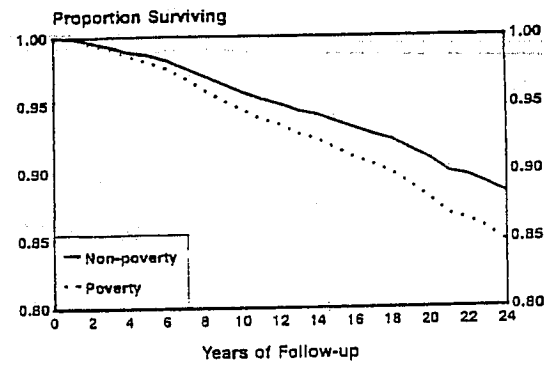


Figure 22

Survival without ischemic heart disease mortality by poverty area residence



With adjustment for age,sex and race

that when we statistically adjusted for age, sex, race, smoking, physical activity, income, education, access to health care, obesity, depression, social isolation, and other variables, those who lived in the poverty area were still at increased risk. The results were little different when we simply adjusted for age, race, and sex.

These results, among others, led us to speculate that there might be properties of the areas in which people live which convey risk, independent of individual characteristics. In some similar analyses, we constructed some scales based on analyses of census tract characteristics and examined whether these characteristics also predicted risk of death (Haan *et al.*, 1989). Figure 23 shows the results from one of these analyses. In this case this scale represents the percent of males who are old, percent housing with no or shared bath, percent housing with no heat, and the percent of widowed males. If you live in a census track which is high on this scale you have a mortality rate about 30-40% higher than if you live in a census track which is low on this scale. Again, this finding persisted after statistical adjustment for dozens of covariates, in various combinations. These studies provide additional evidence that the properties of the area in which we live may be very important in terms of understanding the heterogeneity of mortality risk within the population.

In order to pursue this further, we turned to an examination of the small area variations in health status. Figure 24 shows standardized mortality ratios (SMR) for deaths from all causes for zipcodes in Alameda County California (Kaplan *et al.*, 1991). The SMR is essentially the ratio of observed to expected deaths for each zipcode. In this figure, the SMRs are plotted as altitudes, so a "mountain" corres-

Figure 23

"Old-down" scale items and death rates/100,000 by scale quartiles

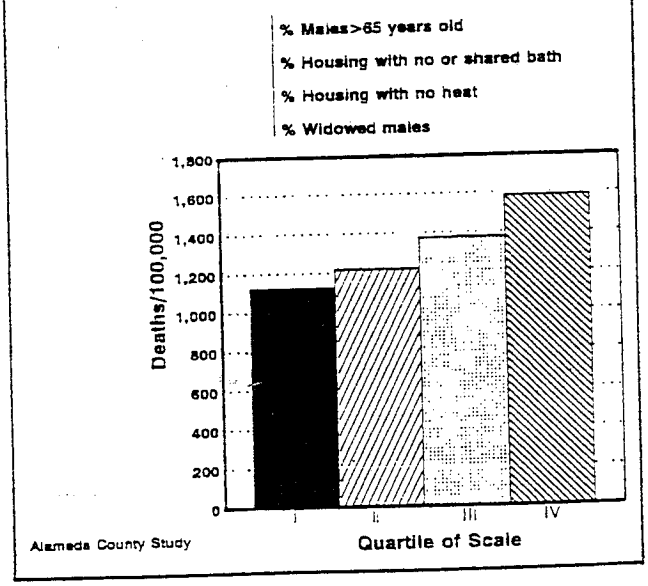
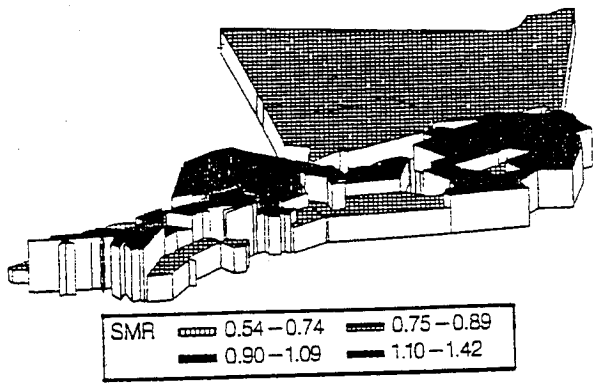


Figure 24

Standardized mortality ratios for Alameda County zipcodes



ponds to an area of high excess mortality. Not surprisingly, we found that mortality is not randomly distributed in the county, and there was a mountain range of excess mortality. The same zones of excess mortality were found whether we looked at mortality among the young or the old, whether we looked at all cause mortality, cardiovascular, or lung cancer mortality, or whether we looked at hospital discharges.

There seem to be health characteristics of areas—while these health characteristics must be composed of the health status of individuals, a focus on the properties of areas leads to a different kind of analysis. For example, when we looked at the factors which were more prevalent in the high versus the low SMR areas, we found many differences. High SMR areas had higher prevalence of low education, being unable to fill a prescription in the last month because of inadequate money, having few friends, living in an unsafe neighborhood, low emotional support, low tangible support, being sedentary, low income, being a crime victim during the last year, having inadequate food at least once a month and being a current smoker.

These findings suggest that we need consider what you might think of as the "ecologic niche" in which individuals live. Our evidence suggests that a wide variety of hazards, at the personal and socioenvironmental level, cluster together in high SMR areas, and we suggest that the totality of these properties, and their interactions, define a unique ecologic niche which may carry with it health consequences. When we combined these characteristics into demands and resources (Table 3), we found that people who live in high SMR areas are ten times more likely to report high levels of demands and low levels of resources.

Table 3

Demands and Resources

Demands

- Daily activity is hard, repetitive, and fast
- Live in unsafe neighborhood
- Crime victim
- Poor health
- Inadequate money for food, medicine, or medical care

Resources

- Daily activity involves decision making and control
- Top 60% income
- ≥ High School Education
- Some health insurance
- ≥2 Close friends or relatives
- ≥ Source of emotional support
- ≥ Source of tangible support

These findings support the development of an approach to the socio-environmental conditions in which people live which is not simply focused on individual behaviors but which focuses on the entire complex of behavioral, social, psychological, and socio-environmental properties, and their relevance to the health experience of these individuals. While these are only preliminary findings, it suggests an expansion of the bio-behavioral agenda, perhaps to a consideration of specific patterns of physiologic response to particular types of ecologic settings.

V. Probe Diversity

It goes without saying that we need to do a much better job of looking at diversity in terms

of age, ethnicity, culture, and gender. But, our task extends beyond the now commonplace exhortation to be inclusive of age, race, ethnicity, and gender in our studies. We need to remember that there is considerable overlap between the distributions of risk factors and health measures in all these groups. To the extent that we address this situation by talking simply about men and women, young and old, blacks, Hispanics, whites, or other groups, we really lose substantial explanatory power. Our focus needs to include all groups in order to fully sample the heterogeneity of both the risk factor and health experience in the population. But, in addition, we need to be cognizant of the substantial heterogeneity within groups, the substantial overlap between groups, and the analytic imperative to examine contributors to both within and between group differences.

VI. What are the Public Health Implications of Bio-Behavioral Research?

We need to continually examine the public health implications of bio-behavioral research and its presentation to the public. The public is bombarded by information. They do not know the significance of it, they do not know who to believe, and they do not know if what they read about hostility or type A or depression or smoking or alcohol consumption or aspirin is true.

I believe it is the responsibility of bio-behavioral researchers to provide a context or metric by which to interpret findings. There are some very simple metrics that one can use: how much is the public's health can be explained by factor X; can the factor be modified; how important is the factor relative to other factors? To maintain our credibility with the public we need to develop metrics which allow us to determine the extent to which we are talking about phenomenon which have a broad public health significance.

Now these are not simple tasks, they are quite complex; but behavioral, social, psychologic, and socio-environmental factors are at the heart of the public's health, influencing virtually every aspect of physical and mental health. This is a fact which will not be modified by molecular biology. To ignore this complexity is to trivialize the true contributions that studies of the behavioral and social foundations of health can make and to impair our ability to deliver on our obligation to develop bio-behavioral knowledge in service of improvements in the public's health.

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