the Numerator

Department of Epidemiology • University of North Carolina at Chapel Hill • Vol. 3, No. 1

International Visiting Scholars

Four international Visiting Scholars are with us this year:

- Dr. Rodney Jackson, from New Zealand
- Dr. Eduardo Mota, from Brazil
- Dr. Jong-Ku Park, from Korea
- Dr. Tosiya Sato, from Japan

Drs. Jackson, Park and Sato are working with the cardiovascular disease faculty, and Dr. Mota is working in infectious disease epidemiology.

Good News, Bad News on the Faculty List

Welcome to three full-time faculty members who joined us this year:

- Dr. Dana Loomis, Occupational/Environmental Epidemiology
- Dr. Joellen Schildkraut, Cancer Epidemiology
- Dr. James Thomas, Infectious Disease Epidemiology

But sad to lose two of our psychosocial faculty:

- Dr. Sherman James to the University of Michigan, Ann Arbor
- Dr. David Strogatz to SUNY, Albany

A Successful Gathering at Birmingham

About 45 UNC alumni, students and faculty gathered at SER, in the Birmingham Hilton last June 15. We talked, we networked, we enjoyed the food and drink, we enjoyed each other. Plan to join us in Snowbird, Utah, next June.

Notes from the Chair

Nineteen ninety is starting with great excitement and promise for the Epidemiology Department and, more broadly, the School of Public Health at the University of North Carolina at Chapel Hill. We are starting the new decade by moving into a new building, located directly behind Rosenau Hall, which nearly doubles our previous office space. All of our full time faculty have offices in this single location, but staff for most of our research projects will continue to be housed in the NCNB building in downtown Chapel Hill.

Another landmark development for our Department is the addition of laboratory space. Laboratories were last a feature of the Epidemiology Department in 1971. The reason that laboratories are vitally needed relates to the growth of the infectious disease program within the Department. This component of the Department has developed and flourished in response to internal pressures — the requests from Epidemiology students — and from the changing environment outside of the Department. Specifically, the School of Public Health is developing an infectious disease program, which cuts across several departments including our own. The influence of disease trends, nationally and internationally, in sexually transmitted diseases and AIDS is a strong external influence on our growth in infectious diseases. Furthermore, a growing body of international students is applying to our Department, and for them, infectious diseases are a major threat to the health of their countries' populations.

Another set of interests within the Department also requires laboratory capability. These include the converging interests in biological markers arising from our epidemiologic studies in cancer, reproductive events, and environmental and occupational exposures. Some of these markers require extremely sophisticated assays of molecular or chemical events, e.g., DNA adducts, whereas other assays, such as micronuclei in cellular specimens, have been learned (with expert assistance) and accomplished by doctoral students in our Department. We anticipate that growth in the laboratory sciences as an underpinning for chronic disease epidemiology (as well as infectious disease epidemiology) will be a major thrust for the 1990s. Our Department should be a leader in this development.

The official ceremonies opening and announcing the new Public Health and Environmental Sciences Center, McGavran-Greenberg Hall, will take place on May 4 at the time of the School's 1990 Alumni Conference. The focus of this conference is "Bridging the Gap Between Research and Service: Challenges for the 1990s." Faculty in the Epidemiology Department are working with representatives from other units of the school to make this an exciting and rewarding occasion for all attendees. All of us in Epidemiology look forward to seeing and greeting our alumni at this truly historical event.

The Cholesterol Story:

UNC Contributions (1959-1989)

by H. A. Tyroler, M.D.
Alumni Distinguished
Professor of Epidemiology

A large number of faculty, visiting scientists, post-doctoral fellows, trainees in the cardiovascular epidemiology doctoral program and other alumni have investigated the cholesterol - coronary heart disease relationship since the founding of our department in 1959. I shall present some highlights of our history, their relation to the current cholesterol controversy in the lay press and conclude with projections for the future. The contributions of all our epidemiologists will be discussed without identification of any individual.

Early in the development of the department we conceptualized the modern epidemic of coronary heart disease as arising from rapid social changes: predominantly rural, agrarian, manually laboring societies with traditional values were transformed to more affluent, urbanized, industrialized, predominantly sedentary societies without preparation for adaptation. Diets high in total calories, saturated fats and cholesterol became generally available whereas energy expenditure and physical activity decreased, with resultant population elevations in serum total and low density lipoprotein cholesterol. We tested these hypotheses in communities in the U.S. southeast (western North Carolina, Evans County, Georgia, Charleston, South Carolina), in the U.S. southwest (Papago Indian reservation) and in the southwest Pacific Island migrants to New Zealand, while related studies among migrants from Japan to Hawaii to the United States, and Ancel Keys' Seven Countries studies, were confirming the association of dietary factors with serum cholesterol and coronary heart disease. Cohort studies in Evans and Charleston Counties added to the individual risk factor information derived from the Framingham and the Pooling Project studies. Both for individuals and at the aggregate level of communities, the results of epidemiologic studies were consistent with experimental animal studies of progression and regression of atherosclerosis. These studies contributed to statements by the American Heart Association and its Council on Epidemiology that mass coronary heart disease required a population distribution of total serum cholesterol shifted toward higher values.

Recommendations for modification of levels of total serum cholesterol in populations were advanced decades ago. However, government level recommendations were withheld in the absence of evidence from clinical trials of efficacy of lowering total serum cholesterol. Although trials of serum cholesterol lowering had been performed and in aggregate suggested efficacy (based on meta analyses or quantitative overviews) individual trials were not regarded as definitive until the results of the Lipid Research Coronary Primary Prevention Trial became available in 1984. The coordinating center for this historic, large scale, multi-center trial was in the UNC Department of Biostatistics, and members of the Department of Epidemiology collaborated in both the trial and an associated series of community-based epidemiologic surveys. The results of these studies forcibly confirmed the central role of total serum cholesterol and of low-density lipoprotein cholesterol as its atherogenic component, and of high-density lipoprotein cholesterol as protective.

We demonstrated striking similarity between the risk function relating levels of total serum cholesterol to ischaemic heart disease in populations, and the reduction in risk in the aggregate, quantitative, overview of the completed randomized controlled trials. A National Heart Lung and Blood Institute sponsored consensus conference (in which members of the Department of Biostatistics and the Department of Epidemiology of UNC participated) judged that the cumulative evidence indicated not only the etiologic role of cholesterol, but provided convincing evidence that lowering total serum cholesterol, and particularly low-density lipoprotein cholesterol, reduced the risk of coronary heart disease . Subsequently, numerous consensus conferences in many parts of the world arrived at generally similar evaluations of the evidence, and made generally similar recommendations for interventive action.

One such action has been the development of the National Cholesterol Education Program in the United States. The US has arrived at its present commitment to actions designed to translate basic and epidemiologic scientific knowledge into clinical and community practice for the control of serum cholesterol levels, with the goal of reducing the burden of coronary heart disease.

In contrast to the emerging worldwide scientific consensus and policy makers' recommendations regarding cholesterol, controversy recently has arisen in the lay press stimulated by the provocative article **"The Cholesterol Myth"** by Thomas J. Moore published in the Atlantic Monthly. The factual content reported in this article is generally accurate although often taken out of context. However, the interpretation and inferences drawn therefrom are not valid and there are glaring omissions of facts that are not supportive of the author's thesis. Moore argues that cholesterol modification does not affect coronary heart disease risk. This is based on a critique of clinical trials, each considered separately; however, the results of the trials when analyzed in aggregate overwhelmingly demonstrate efficacy. Furthermore, the article ignores the epidemiologic observational literature of migrant populations and populations of nonmigrants exposed to environmental changes, circumstances leading to changes in serum cholesterol and associated changes in coronary heart disease risk. Moore's contention that dietary intervention does not change cholesterol levels and does not modify coronary heart disease risk is at variance with the collective, aggregate evidence of

the clinical trials and the observational literature. He argues that drugs are not safe and that efficacy and safety in women and the elderly have not been determined and this is partially correct. All drugs have associated side effects and toxicity. The question is safety in relation to efficacy and favorable results to date are clear for coronary risk reduction. However, the available clinical trials data for pharmacologic treatment are based upon relatively short-term follow-up of selected groups and long-term follow-up will be necessary, in order to answer these questions satisfactorily.

Moore's argument that clinical trials of serum cholesterol lowering have not demonstrated prolongation of life expectation is factually correct. However, he ignores the fact that each of the individual primary prevention trials was not designed, and did not have the power, to detect an increase in survival as a primary endpoint. The aggregate evidence, while not showing prolongation of life, does not demonstrate any consistent excess in deaths due to non cardiovascular causes. Moore also does not address the natural experience of populations (such as the Japanese) whose traditional diets result in levels of serum cholesterol much lower than those of the US with attendant lower rates of coronary heart disease, in whom all-cause mortality is as low or lower than in the U.S., although he does cite excesses in diseases such as stroke. Finally, based on the clinical trials, Moore argues that the cholesterol interventions are not cost effective, citing in particular the extremely high cost of carrying out the LRC-CPPT. This was a research oriented activity, a double blind trial, one in which the reduction in cholesterol was much lower than could be achieved with currently available, more effective, lipid lowering drugs under clinical circumstances with feedback to patients and physicians and modification of treatment strategies based on patient responses. The cost-effectiveness estimates are much lower when different models are used, and particularly when population intervention strategies are considered. On balance, the only argument of Moore which is irrefutable is that pharmacologic lowering of cholesterol has not to date produced demonstrable prolongation of life in controlled clinical trials.

The cumulative evidence from the basic sciences, molecular genetics, clinical trials and epidemiology, evaluated by scientific bodies in many countries, varies dramatically from the opinions of a few individuals expressed recently in the medical and lay press. The scientific reviews have led to consensus statements and national policies (to which UNC faculty have contributed). The recommendations are for joint, simultaneous, coordinated approaches to modify total serum cholesterol both by a high risk and a community-oriented approach. The high risk strategy is designed to detect, diagnose, and evaluate elevated cholesterol in individuals and to modify elevated levels by appropriate individualized interventions. Additional, strong evidence supporting this approach was recently provided by the reports of three clinical trials of lipid lowering resulting in regression of coronary artery atherosclerosis.

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Regression was achieved by each of three different drug regimens and also by vigorous, non-pharmacologic means. Dietary modification is recommended in all high risk individuals and it has been estimated that more than 90 percent of hypercholesterolemics can have their cholesterol levels reduced to goal levels by diet alone. Simultaneously, a community-oriented approach is advocated to change the total distribution of serum cholesterol in the population towards lower levels. Specific recommendations from the National Cholesterol Education Program to achieve this goal are expected shortly. Dietary modifications both of high risk individuals and at the general population level undoubtedly will be advocated, as they have been by various bodies such as the American Heart Association in the past.

While emphasizing the underlying importance of serum cholesterol, there also is recognition of the multifactorial origin of atherosclerosis and coronary heart disease. Investigative and intervention approaches to other risk factors are an essential part of any program of coronary heart disease control. Currently, members of our Department are collaborating in investigative studies at levels extending from the molecular genetic (e.g. the investigation of genetically determined polymorphisms of apolipoproteins influencing the risk of CHD) to the global (e.g. studies comparing the relation of social factors to serum cholesterol levels in populations among more than 30 countries in the World Health Organization's MONICA project and the Atherosclerosis Risk in Communities Study in four communities in the United States). Current investigations at UNC are focusing on the precursors of atherosclerosis to provide knowledge permitting primordial prevention, while simultaneously collaborating in clinical trials of intervention at the individual level and community intervention trials at the population level.

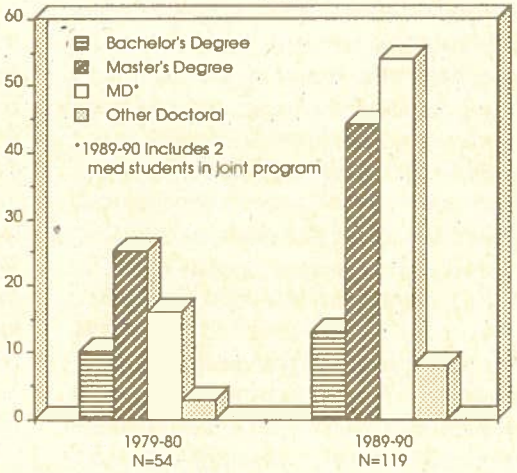
Coronary heart disease mortality has declined more than 40% in the United States since its peak in the mid 1960s. A portion of that decline is in all likelihood attributable to changes in lifestyle associated with the research effort described above. We are now investigating societal level determinants of the decline, many of which appear different from those earlier responsible for the ascending limb of the epidemic. Meanwhile, coronary heart disease mortality remains the single leading cause of death in the United States. Continuing epidemiologic research and community interventions, combined with basic science and clinical efforts, offer promise for elimination of this disease as a mass epidemic phenomenon.

At the End of a Decade:

A Bigger, More Diverse Enrollment.

Changes in the department during the past ten years reflect significant changes in national and international health concerns. The past decade has brought changes in the composition of the student body. We have more than doubled in number. We include more physicians, students from more diverse backgrounds, and the percentage of international students has doubled (to approximately 12%). We are active in more areas of research.

Prior Degree Held by Epidemiology Students

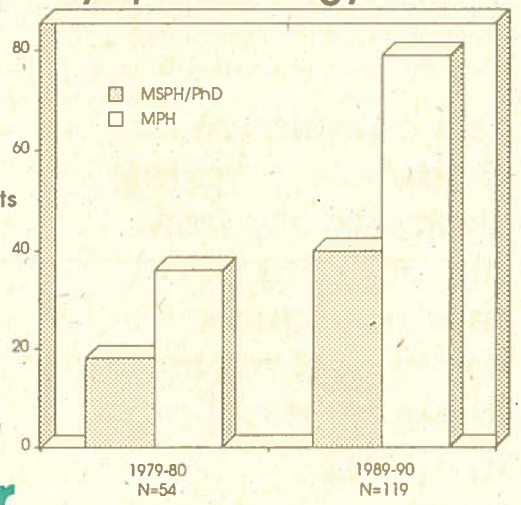


Student's Research Areas

(1979-80):
Environmental/Occupational
Health Services/Clinical
Cardiovascular
Psychosocial
Cancer
Population/Family Planning

(1989-90):
Health Services/Clinical
Cancer
Cardiovascular
Reproductive
Infectious Disease
Pharmacoepidemiology
Health Promotion/Disease Prevention
Environmental/Occupational
Social/Behavioral
Dental
Genetic
Methods

Type of Degree Sought by Epidemiology Students



Liaison Programs

Several select groups of research-minded physicians, dentists and veterinarians enter degree programs in epidemiology each year under the auspices of one of our liaison programs. These liaisons provide research settings and support degree work in epidemiology for physicians, dentists and veterinarians. Currently 21 students are enrolled in the department through one of these programs.

Since the establishment at UNC of the Robert Wood Johnson Clinical Scholars in 1974, our list of liaison programs has expanded to eight. In addition to the Clinical Scholars, we now have the Preventive Medicine Residency program, the Primary Care Research Fellowship, the Dentist Scientist program, the Program in Oral Epidemiology, the International Clinical Epidemiology Network (INCLEN), the Duke Occupational Medicine Residency program, and the North Carolina State University Veterinary Medicine Postgraduate program.

The liaisons have provided outstanding students over the years, and have led to some valuable links with the affiliated schools and departments. Most of the alumni go on to academic positions, and many have retained strong working connections with the Department of Epidemiology.

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