

**INTERNATIONAL STUDIES:
CONTRASTING CULTURES**

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An essence of epidemiology is the search for etiology under conditions of contrast and variation. Our CVD Epi pioneers and leaders understood this. For example, at the 1954 World Congress of Cardiology, where CVD epidemiology first arrived in the medical mainstream, Jerry Morris opined:

“The search for large-scale nutrient factors inside Britain . . . may not be rewarding: the amounts of fats now consumed in different levels of income are similar. Inquiry is likely to make progress if it is extended to include comparisons among different societies.”

[Early diet-heart investigators might well have profited from this counsel.]

Cultural comparisons involve most of Morris’s Seven uses of Epidemiology, but particularly relate to the last:

VII The Search for Causes

Morris summarizes, in his little book, ‘Uses of Epidemiology’:

“One of the most urgent social needs of the day is to identify rules of healthy living that might reduce the burden of the metabolic, malignant and ‘degenerative’ diseases which are so characteristic a feature of our society. This is the main field today for the use of epidemiology.”

He goes on to say: “. . . the problem is . . . to state a question correctly and then to choose the most direct and economical method of trying to reach an answer. In some instances prospective inquiry is clearly necessary, in others a retrospective study is more appropriate.” Often, clues and confirmation come from contrasting cultures. He advises: A “main function of epidemiology is to find and compare high and low rate populations” [to arrive at postulates of cause].

JN Morris: Uses of Epidemiology. Livingstone; London; 1957

SLIDE: TC Distributions. The Essence of Comparisons among cultures

Several studies come to mind in which contrasting cultures were effectively explored to test hypotheses of cause in coronary disease. Early on were the Seven Countries Study and NIHONSAN, and more recently, MONICA, and INTERSALT. Other and independent cultural comparisons also contributed crucially to the evolution of views of cause and prevention.

But let’s go back a little to Prehistory, that is, before formal, population-based CVD epidemiological studies.

A few of us are actively involved in analyzing the historical development of our field; several people here today contribute importantly to this effort. We invite you and seek from you particular anecdotes, unique documents, and historic photographs to illuminate and enliven this effort.

We tackle this major undertaking with pleasure and dedication because we believe that knowledge of the history of this research, with a greater understanding of the cultural background of disease trends and health disparities, are central to our effectiveness as a discipline. They are essential to sound health policy, just as they are for policy among nations.

SLIDES; Uniqueness of CVD Epidemiology

First a little musing on the importance of our history and on the uniqueness of CVD prevention research.

PREHISTORY: Slide of three streams of converging knowledge.

We rest on the shoulders of many foresighted giants. For example, our history team is trying now to run down a suggestion that the curiosity of two pioneers of vascular pathology, Ignatowsky and Anitchkov, of the Imperial Military Institute in St. Petersburg, who took up the experimental feeding of animal foods to herbivores, was aroused by their observations of cultural contrasts among their "clients" in the autopsy theater. The well-off Czarist elite and the subsistence conditions of the Russian peasants represented a huge cultural contrast in diet and lifestyle.

As you recall, they fed rabbits animal diets like those of the human elite. This rapidly killed the rabbits. When smaller doses of dairy products and horse meat were added to vegetable rabbit chow, the herbivores survived long enough to develop renal and arterial lesions. The latter were found eventually to be cholesterol rich and this proved due to animal lipid in the diet rather than to protein.

SLIDE Katz and Stamler on the importance of experimental pathology.

MEDICAL MARCO POLOS

SLIDE: DE LANGEN

But, should this story prove apochryphal, that of enlightened curiosity and experiment derived from observed cultural contrasts, we have a well-documented saga to recount about a true pioneer in CVD prevention research. This was a Dutchman, an unsung hero whose reputation was recently revived by colleagues Kesteloot and Kromhout; their countryman, Cornelis Delangen. We believe that Delangen was among the first Medical Marco Polos to travel, observe, experiment and then pull together the clinical, the metabolic, and the population picture about diet, lifestyle and CVD. And remarkably, he did this in Java between 1915 and 1925!

Tell Delangen Story:

His ward/his biochemical background/his contrasting cultures/systematic observation/diet experiments/

This sentinel contribution of Delangen, based on cultural contrasts, transpired toward the end of the Dutch colonial period, during which time Dutch clinical investigators thought little about publishing outside the Dutch literature. Delangen would surely have been less an unsung hero had he published in English, which many of his Dutch contemporaries and successors did.

SLIDE: SNAPPER: CHINESE LESSONS TO WESTERN MEDICINE

For example, Isidore Snapper was a close colleague and lifelong correspondent of Delangen and trained in the same department of medicine, that of Van den Bergh at Groningen. Snapper foresaw the Nazi danger in the 1930s and took a Rockefeller Fellowship at Columbia U. and from thence went to that foundation's collaborative program with Peking Union Medical College. He carried the same kind of skills, curiosity, and broad view as had Delangen to observations among the Chinese and in his well-known 1941 volume, "Chinese Lessons to Western Medicine," made these historic suggestions about diet and CVD:

"Quantitative and qualitative differences exist between the lipid content of the Chinese and the foreign diets . . . The Chinese diet contains only small amounts of cholesterol but considerable quantities of unsaturated acids, especially of linoleic and linolenic acid. It is certain the the average choleterol content of the blood of the Chinese is lower than that of Westerners and this gives perhaps an indication why the tendency to lipid infiltration of the vessel wall is so much smaller among the Chinese."

In the second (1965) edition of his volume he made more insightful suggestions about vegetable oils and unsaturated fatty acids:

"Here it should be pointed out that the fatty acids present in vegetable oils are completely different from the fatty acids in butter. This difference may perhaps be considered as a point in favor of the Chinese way of preparing the food."

He concludes: "Any suggestion about a relation between the presence of special unsaturated fatty acids in the diet and the remarkable scarcity in China of several diseases, in the pathogenesis of which lipoides play an important role – as arteriosclerosis, Gaucher's Disease, disseminated sclerosis, gall stones, perhaps even thrombophlebitis – would be completely speculative. It should, for instance, be emphasized that in Dutch East India the diseases mentioned are also very infrequent. . . Even so it must be considered [that] the variations in diets in different parts of the world, as far as the fatty acid content is concerned, may influence certain diseases which depend on the composition of the phospholipids of the tissues."

CONCLUSION:

So these Dutch investigator-Mafiosi became a dynasty in early CVD epidemiology, a dynasty unbroken today because Juda Groen, colleague of Delangen and Snapper (who early contrasted Sephardi and Ashkenazi tribes in Israel, and Trappist and Benedictine monks in Holland), was on the examining committee for Daan Kromhout's thesis. Thus, Groen takes us directly back to Delangen and van den Bergh, while Kromhout brings us forward to contemporary

Dutch and international leadership, particularly in our topic this afternoon; studies among contrasting cultures.

I recall that at the outset of his explorations in the early 1950s, Ancel Keys talked about Delangen, Snapper, and Groen. Because of Keys's early writings (the first "mode of life" paper was in his talk to the Chicago Heart Association in 1948), he was invited in 1952 to a medical conference on diabetes and nutrition in Amsterdam. At that period, he had already begun the romantic era of peripatetic informal cultural comparisons in Italy and Spain, South Africa and Japan. His already well-formulated hypothesis about lifestyle, diet, and coronary disease was roundly attacked and rejected by most of his confreres at that Dutch meeting.

Now, you should know that Ancel Keys reacts vigorously but usually quite effectively following such attacks. He sees the light and begins to plan more definitive studies, including cultural comparisons and metabolic ward experiments, to produce still more credible evidence. The rest is history.

Shortly after the Amsterdam meeting, Ancel was invited to Mt. Sinai in New York by the distinguished internist Ernst Boas (son of the noted anthropologist Franz Boas), where the same talk and diet-heart thesis was accepted and as roundly applauded as it was rejected in Amsterdam.

There, as Ancel immodestly claimed in his memoir, Fred Epstein became a disciple. In fact, Boas and Epstein at the Sidney Hilman Center were already in 1952 into their own design of a pioneering investigation of cultural contrasts in lifestyle, comparing CHD and risk factors among Italian and Jewish garment workers in NYC. This was, I believe, the first systematic, population-based cross-cultural comparison, and we will touch on it shortly.

MORE MARCO POLOS

SLIDE Keys and White in Italy

We have labeled these several early observers "Medical Marco Polos." They travelled widely, at first making fortuitous observations, soon asking particular questions, and eventually developing a formal research strategy comparing populations and carrying out supportive bench and clinical work. Ancel Keys and Paul White were among those pioneers we particularly recognize as founding fathers of CVD Epidemiology and Preventive Cardiology. They clearly got an early impetus to their ideas from field observations of cultural contrasts, population differences, and of population changes over time.

Keys and White Early Cultural Comparisons

THEIR Story: Oxford/FAO/Bergami/Naples/PDW/Spain/Sardinia/S. Africa/Japan/Ilomantsi story

SLIDE: World Congress of Cardiology, 1954, where cvd epi became mainstream

EARLY FORMAL CULTURAL COMPARISONS

**New York City Garment Workers: Italian:Jewish
Trappist/Benedictine Monks
Israeli Sephardi-Ashkenazi comparisons
Framingham/Yugoslavia
Framingham/Honolulu/Puerto Rico**

These, among others, were early, innovative, and dramatic comparisons among defined populations with early attention to methods. They added to the causal evidence, the concepts and the research strategy for CVD Epi.

I will say more about the Garment Workers Study because it was undertaken by our special pioneer colleague, Fred Epstein, because it was sound and population-based, and because of an unsung hero, his colleague and head of the workers health service, the Sidney Hillman Center, Ernst Boas:

[Epstein, FH and EP Boas: The prevalence of manifest atherosclerosis among randomly chosen Italian and Jewish garment workers. A preliminary report. J. Gerontology 10:331-337, 1955.]

I believe it to be the first formal epidemiological study comparing cultures, initiated in the early 1950s, a randomly chosen and representative population of the New York City garment workers union with appropriate sampling, standard methods and quality control. The combined prevalence of coronary disease, cerebral arterial disease and aortic calcification was ascertained in about 500 men and 400 women, along with a number of risk characteristics. Frequency was sufficient to find significantly more coronary disease in Jewish than Italian workers, higher total cholesterol levels in Jewish men and women, and a comparable diet fat intake of 35 percent. Aortic atherosclerosis was as great in women as in men, and age trends were found in serum lipids. The lipid findings confirmed an earlier one by Groen et al. comparing Jewish and Gentile blood donors in the Netherlands.

[Groen, J, Kamminga,CE, Reisel, JH, and Willebrands, AF: Cholesterol content of blood serum from Jewish and Gentile blood donors. Neder.tijdschr.v.geneesk., 94: 728-738, 1950]

Now, before moving on to the cohort studies that formalized CVD epidemiology as a discipline, I mention the use of vital statistics on causes of death as an early and important approach to our topic of cultural comparisons.

VITAL STATISTICS ON CAUSES OF DEATH

SLIDE MALMROS article, mortality and diet data

A seminal report in 1950 called attention to the apparent fall in atherosclerosis deaths during WW II and their prompt rebound to epidemic levels among men following the war.

Tell Malmros story/distinguish internist/metabolic sophisticated/finger in the Swedish system/ assumption it had not changed during war/valid changes deaths/ matched by clear changes consumption. Ancel quick to contact and invite Malmros.

This was a particular use of death data, suggesting dramatic trends, related to a constant medical environ and a changing lifestyle, and with profound implications on preventability for those would could see.

Many approaches were made to international comparisons of CVD rates, but these continued to be considered by most clinicians not worth the paper they were reported on.

To the contrary, said our old friend, Donald Reid at the London School: "The use of comparisons of disease experience in different countries as an approach to problems in etiology has a long and respectful history." He cites two stories about cultural comparisons and then qualifies the approach:

Sir George Baker challenged the common wisdom that the Devonshire colic in the 18th Century was due to the different apples used in making cider in Devon versus those of France. Baker recalled from his travels that the colic in France had been related not to the apples themselves but to adding litharge to sour wine, resulting in lead poisoning and lead colic. His investigation led to the finding that lead vessels were used in storing cider in Devon, apparently achieving the same colicky results. The Marco Polo effect.

Percival Potts, who described scrotal cancer as "chimney sweeps' disease," arrived at his idea from noting relatively high rates of the disease reported among chimney sweeps in England and low rates among their occupational cohorts on the Continent. He hypothesized that the disparity was due to hard coal used in England and brown coal used on the Continent. On closer consideration it turned out that it was rather the low standard of protective clothing and personal hygiene of the English chimney sweeps affecting their coal tar exposure, compared to their contemporaries in other countries.

International comparisons of statistical reports on the causes of death have long been dismissed by clinicians as worthless; they should know after all since they fill out the death certificates! I can no longer find the source of the comment by one of our more thoughtful and literary American scientists, Louis Thomas, who once sardonically defined epidemiology as "leafing through death certificates." I have enjoyed his books and essays but have never forgiven him for that careless thought and language.

Those of us in the cardiovascular field since the 1950s clearly recall arguments that the post-WW II epidemic of coronary disease was almost entirely explained by improved recognition of the disease. This was the opinion of outstanding cardiologists. The closer to the United Kingdom, the stronger that opinion.

Two principal questions arise in the use of vital statistics: are the differences real; and if real, what are their explanations?

We all know the problem of national habits of diagnosis influencing such comparisons. I concurred with our colleague Jean Himbert in Paris in 1971, after inspecting death reports he was examining, in concluding that the French clinician's use of the wastebasket term "cardiosclerosis," was probably responsible for the under-reporting of coronary disease in France. That turned out to be almost surely inaccurate and incomplete, but, as Ducimetiere points out, there may be a French difference but it is not a paradox; disease follows risk in the same way in France as elsewhere. MONICA demonstrated that rates in Alsace resembled those in Bavaria, in Toulouse, those in Italy, and in Lille, those in Belgium.

Another issue in comparison of death rates is the different habits of nosologists classifying disease by the International List, but this is certainly less important than physicians' diagnostic vagaries. Studies comparing the U.S. and U.K. and Norwegian death certification undertaken by Donald Reid and others suggest that cultural differences between broad groupings of CVD diagnoses, such as all heart or all CVD, should not be dismissed as artifact.

International comparisons of death rates and trends is a very important source of hypothesis generation in our field. Certainly they contributed to hypotheses about diet and coronary disease, diet and hypertension, smoking and lung cancer, and about diet, salt, gastric cancer, and stroke (in the hands of a master of death trend analysis, Joseph Joossens).

Donald Reid maintained in the end that, "Inevitably, correlation studies in international mortality are at best a useful source of informed speculation." Of course, it is the collateral evidence, and it is the congruence of evidence from the laboratory and the clinic with the population data and vital statistics that have led to establishment of the diet-heart theory and the risk factor paradigm within which we have investigated and practiced so profitably over the last 40 or so years.

[The pitfall of inferring a common cause when there is a correlation among mortality statistics and risk factors or a correlation between two causes of mortality has, nevertheless, been exposed by case-control and prospective inquiries. For example, in our pooling study led by Geoff Rose, if high fat diet is related ecologically to colon cancer, it seems very likely it is not related through the mechanism of a high cholesterol level.]

SLIDES on comparative death rates

EPSTEIN-THOM STUDIES. VITAL STATS. TO THE Nth POWER

Finally, no one has more carefully and innovatively analyzed reported differences in coronary and all-cause death rates from international vital statistics than the team of Tom Thom and Fred Epstein at NHLBI. They have asked interesting questions and their displays require study, not being immediately obvious. For example:

Figure 2 depicts the trends for heart disease in 6 periods from 1950 to 1978 for men and women in 26 countries, arrayed from the highest to lowest 1950s rates for men. They show congruent patterns by sex in the US and Canada for example,

and opposite directions with men increasing and women decreasing in Ireland, for example.

SLIDE

This interesting display of 15-year changes in heart disease rates for men on the ordinate and women on the abscissa shows in the same 26 countries, where, in the LL quadrant rates are falling for both sexes, as in North America, and on the upper right rising for both as in Portugal and Yugoslavia, and then those where rates are rising for men and falling for women.

They make other displays of the change in proportion of cardiac deaths to all-cause deaths, and sex ratios that show a widening of the sex gap and the north/south gap in cardiac death rates. They show the consistent international ranking of countries in cardiac death rates over time, which remains constant even when absolute rates change. Another display shows the trends for cancer deaths in women, and what happens when you remove the soaring rates for the one cancer having a specific known cause, lung vs. cigarettes. All-cancer death rates then show improvement as in CVD deaths, not seen when lung cancer is included in the totals. And so on.

Joossens and Kesteloot have provoked us with comparable intellectual challenges in their analyses of French versus Flemish death rates in Belgium.

FORMAL POPULATION-BASED INTERNATIONAL POPULATION STUDIES: CULTURAL COMPARISONS:

The prototype of the international cohort study is the Seven Countries Study. But it was not alone among international cohorts:

Framingham/Yugoslavia

Framingham/Honolulu/Puerto Rico

The FINE Study (Finland and Netherlands)

OTHERS?

THE SEVEN COUNTRIES STUDY/SLIDES

Seven Countries is the only one for which I have pretty slides. Jerry says he has been remiss in getting photo-documentation of his far-flung INTER-EVERYTHING STUDIES. I hope some of his colleagues here will want to get their good examples into our history effort and on the history website that should be up and running next year. I suppose we could get some dramatic shots of the Yanomamas, an Intersalt population, from National Geographic or from Jim Neel!

SLIDE: MIGRANT STUDIES;NIHONSAN

The effects of Switching Cultures, that is migrant studies, came along chronologically here, before the modern period of cross-cultural surveys that we will get to shortly, such as MONICA/INTERSALT/
INTERMAP/INTERLIPID/INTERHEART

Migrant studies are a special case of international population comparisons in which peoples of presumably the same genetic stock, living in the same environment, migrate to a different environment and are found rather soon to achieve a different

frequency of risk characteristics and incidence of disease. We will only touch on one classic study in that regard, NIHONSAN, though there have been several such:
Boston Brothers' Study: Fred Stare et al.
Norway/UK/US Migrant Study: Donald Reid et al.
Tokelau/NZ Migrant Study: Ian Prior et al
Australian Aborigenes go home : Kerin O'Dea.

The questions addressed in migrant studies involve differences in disease frequency, either prevalence or incidence, upon acculturation and exposure to a new culture, and whether there is relative protection by early residence in a favorable environment, etc. Whether this is from a continuation of early habits is the question.

We won't dwell on selection in populations of migrants. They are likely more enterprising, more fit, on one hand, or have more instability or vulnerability to economic pressures (such as the Irish migration in the 19th Century from the poorest regions of the island). Moreover, migrants undergo some sort of medical screening on leaving or arrival, which again makes them a select population rather than representative of the old country.

Some of these issues have been approached by examining siblings that have remained in the old country versus those who migrated, for example, between Norway and the U.K. and between Ireland and Boston.

The prototype migrant study, NIHONSAN, arose from the observation that stroke was a major cause of death in Japan and seemed to be less common among Japanese in Hawaii and California, with just the opposite being true for coronary deaths. This was confirmed by differences in death certificate reporting by Tavia Gordon and led, at the suggestion of Stallones, to surveys of more or less representative populations in Japan, Honolulu and San Francisco. Bias was reduced by standardizing diagnoses and risk factor measurements.

The trends for laboratory values were consistent for serum glucose, triglycerides, and serum cholesterol but the cross-sectional risk factor findings did not explain the difference in coronary prevalence rates and so longitudinal studies were undertaken in the Hawaii and Japan mainland populations.

Such findings, according to Donald Reid, "Reveal the abiding need for imagination in conception, perseverance in conduct, and above all, an acceptance of the discipline of standard methods and centralized control over a long period."

Results;

There was, indeed, a gradient in coronary heart disease prevalence by standard assessment, from 5.3/1000 in Japan and 5.2 in Hawaii, to 10.8/1,000 in California. Rates for definite plus possible CHD were 25, 35, and 45 respectively. Of risk factors, only serum cholesterol showed the same gradient as CHD. Hypertension was intermediate in Japan and Hawaii and highest in California. But at the same level of blood pressure and cholesterol, there was a greater prevalence of coronary disease in California.

The authors concluded, "These facts, plus a near universality of smoking in Japan, suggests that conventional risk factors only partly explain the observed gradient in coronary heart disease."

[That confident conclusion, perhaps ignoring the possibility of necessary and contributory causes for population contrasts, was made in 1974 by our colleague, the already-budding Social Epidemiologist, M. Marmot. It ignores the possibility of a necessary factor in the population differences: diet.]

[Marmot MG, Syme SL, Kagen A, Kato H, Kohen JB, Belsky J. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: prevalence of coronary and hypertensive heart disease and associated risk factors. *American Journal of Epidemiology*, Vol 102, page 514-525, 1975.]

At this early stage and maybe with a skeptical attitude about biomarkers in the first place, they concluded further that, "...[when] cholesterol, blood pressure and smoking differences do not completely explain these gradients in cardiovascular disease, then we must look elsewhere for explanations." They proposed that one "elsewhere" might be genetic factors in the migrant Japanese. Here one would have to postulate that those with genetically predetermined intermediate eventual risk got off the boat in Hawaii while those with higher genetic risk continued the voyage to San Francisco.

In fact, of course, the Japanese in America, "Eat different diets, they have different patterns of occupation, [and] they live in a different social and cultural milieu than Japanese in the home country."

MODERN CROSS-SECTIONAL, CROSS-CULTURAL CORRELATES: INTERSALT

Stamler, J, 1997. The INTERSALT Study: background, methods, findings, and implications. *American Journal of Clinical Nutrition*. 65(2 Suppl):626S-642S.

Key Words sodium, salt intake, blood pressure, INTERSALT Study, cardiovascular diseases

The INTERSALT Study focused on high sodium intake as one of several exposures producing high blood pressure in adults aged more than 35 years. It was intended to fill the gap in the research left by small-scale, short-term preceding studies that often lacked valid measures of salt intake.

Slide Gliberman Study

The hypotheses explored by the INTERSALT study were that, among a large number of participants, systolic and diastolic blood pressure would be related directly to 24 hour urinary sodium excretion, the ratio of sodium to potassium excreted, body mass index and alcohol intake both directly and independently. Potassium excretion was hypothesized to be inversely related. An inverse association was found with protein and with SES, and the need demonstrated for large

populations and repeat diet measures with correction for within-person variation, and control for multiple variables.

Paul Elliott has brought us up to date on the seminal findings of this remarkable cross-cultural investigation, the essence of sound, innovative, efficient international studies, including the resistance of segments of society to its clear findings. [Stamler articulates the need for more long-term studies that focus on linking nutrient intake and cardiovascular diseases where causality can not yet adequately be inferred.]

INTERMAP

(Stamler, J, P Elliott, B Dennis, AR Dyer, H Kesteloot, K Liu, H ueshima, and BF Zhou for the INTERMAP RESEARCH GROUP. INTERMAP: background, aims, design, methods, and descriptive statistics. *Journal of Human Hypertension* (2003) 17, 591-608.)

The second major example of extension of the Seven Countries Study design for cultural comparisons is INTERMAP of the Stamlers and colleagues internationally. Here they address the cross-cultural role of dietary factors, especially salt and minerals, then macronutrients in hypertension, with particular attention to the patterns found in Black peoples, Asians, and Hispanics compared to whites, in many populations of varied ethnicity and socio-economic status as well as dietary habits In a large sample of 4,700 men and women, 40-59 years of age, from 17 diverse populations in four countries (China, Japan, U.K. and U.S.).

INTERSALT confirmed that salt, alcohol intake, and body mass influence blood pressure directly, potassium intake inversely. INTERMAP takes up from that knowledge and recognizes the independent diet effect on hypertension shown in the DASH trial. INTERMAP looks at the cross-sectional relations of macronutrients and blood pressure over and above the above factors and across diets and cultures.

Hypotheses are posed about the relation to blood pressure of the amount and type of protein, lipids, carbohydrates, amino acids, minerals, antioxidants, fiber, and caffeine. Confounders controlled are BMI, alcohol, sodium, potassium, age, and sex.

[Population samples in 17 areas of 4 countries (US.UK, Japan, and China)) were surveyed with two repeat urine collections and four repeat dietary recalls; blood pressure was measured twice at each of 4 visits; and dietary recall data were converted into nutrients by national databases.]

Estimates of the favorable impact on blood pressure of various improvements in nutrition is assumed to contribute to improved dietary recommendations for the primary prevention of hypertension and for shifting population blood pressure distributions leftward.

Keep in mind that in most epidemiological studies, the between-subject variability is swamped by the high within-subject variability related to biological and measurement errors and exposures such as dietary intake. INTERMAP is designed to minimize within-subject variability and to maximize between-subject variability across a wide range of environment and culture.

The study addresses the previous findings of differences between age groups in Western countries and the north/south gradient within countries, as well as the different associations of blood pressure with diet components.

The hypothesis that protein intake may be negatively associated with blood pressure level and variance is novel and could have major importance with regard to public health recommendations. Our Seven Countries own Noboru Kimura proposed this idea 50 years ago based on the blood pressure and diet findings in fishing and farming villages in Kyushu. I would have added the separate hypothesis that the combination of low protein, high sodium, low potassium intake, would be more strongly related to hypertension and to blood pressure level, than would the opposite; high protein, low salt, with intermediate levels found for the conditions of low protein/ low salt, or high salt/ high protein combined conditions, presuming such populations exist.

It is not my proper role to report INTERMAP findings, but they appear important for the population strategy of prevention of CVD.

Conclusion:

THE findings confirm those of the NIHONSAN and SEVEN COUNTRIES studies while they provide more specifics about the nutrients closely related to cultural disease differences. This enhances the evidence base for culture-specific intervention priorities.

[The basic correlations are incomplete but these findings are clear:

Large East/West differences in dietary macro and micronutrients exist. From other evidence, these differences can account for a substantial proportion of the population differences in blood pressure, cholesterol and disease rates. Specific diet variables can account for up to 2/3rds of blood pressure difference by education and SES class.

Smokers have less healthful dietary patterns, adding another crucial element to interventions among them to reduce disease risk.

Dietary differences of Japanese in Japan and in Hawaii can account for much of their different risk and rates of CVD.]

INTERLIPID??

INTERHEART

(Yusuf, S, S Hawken, S Ounpuu, T Dans, A Avezum, F Laqnas, M McQueen, A Budaj, P Pais, J Varigos, and L Lisheng. Effect of potentially modifiable risk

factors associated with myocardial infarction in 52 countries. The INTERHEART STUDY: a case-control study. Lancet: 364; 937-952, 2004)

The latest wrinkle in international comparisons is one in which risk ratios were sought for the cross-sectional associations of acute myocardial infarction with common risk factors in 15,000 coronary patients in 52 countries. This addresses the question of universality of risk factors, in particular the force of risk factors in countries having a low or middle range of disease frequency and of economic development. This is carried out in the authors' view of an anticipated "Third World Epidemic" of CVD based on rates that have risen in the developing world and now account for 80% of the CVD burden in the world.

They ask the question whether a global strategy based around the importance of the known ("Western") risk factors would be rational and feasible.

SLIDE from Seven Countries: Multivariate RISK IN US AND EUROPE

This idea was early developed by Ancel Keys, who first applied the multivariate coefficients for the risk factors derived from experience in low burden countries of southern Europe versus high frequency northern European cohorts the U.S. cohorts. He found risk factors universal in their ability to discriminate risk within countries having differing absolute rates of disease. The intersect and slope of the risk factor/disease risk regression were, however, quite different among cultures. The slope of risk in the high frequency countries, for the same level of risk score, was twice as steep as in the low frequency areas.

This has long created doubt about the relevance of western risk scores for the underdeveloped populations of the world. It fostered the inappropriate conclusion that "risk factors explain only half the risk," not touching on the issue of "necessary and contributory" causes.

The individual and multivariate risk ratios found, however, were not terribly dissimilar from those found from followup cohort studies in the developed world, though attributable risk was clearly different,

The authors conclude that preventive strategies can be based on similar concerns and causes, if not on similar principles of intervention, and should have comparable potential worldwide to prevent most cases of cardiovascular disease or premature myocardial infarction. Clearly, population attributable risk of a given risk factor varies according to the prevalence of the risk factor. The issue here is whether the variance observed was due to design of the study or population selection and small sample sizes rather than from prevalence of the risk factor.

The consistency with other findings, the large size of the study, its power and precision estimates in subgroups render it important, and the conclusions from all regions of the world and multiple ethnic groups make results generalizable. The PAR suggests that most of premature myocardial infarction is preventable. Smoking and lipids were the two most important worldwide, accounting for 2/3 of the PAR, which confirms the identical findings in longest term follow-up of the Seven Countries.

Diet and blood lipids were clearly the most important risk factor related to a potential worldwide reduction in myocardial infarction. The odds ratio was greater in women for hypertension and diabetes.

They conclude that "smoking avoidance and increased consumption of fruits and vegetables and moderate activity, along with lipid-lowering should be the cornerstone of prevention of coronary heart disease in all populations worldwide." I would add, "Under the condition that increased fruits and vegetable intake replaces calories from saturated fatty acids!"

Another area of international comparisons, that is, to elucidate differences in the natural history of diseases, and which we will not touch on here, includes the different lag times, survival times, and clinical manifestations of disease.

SURVEILLANCE STUDIES

MINNESOTA HEART SURVEY (MHS)

ARIC

MONICA

The MHS proposed in 1977 the systematic ongoing surveillance in our home base, the 7-county Twin Cities, combined with ongoing study of surveillance methodology. Following the Decline Conference in 1978, this idea became official policy in Bethesda and stimulated the WHO undertaking of MONICA.

MONICA was a grand concept carried out well, and recently elegantly reported. The goal was to measure CVD trends in contrasting cultures and their relation to changes in risk factors, cardiac care, and socio-economic developments. It was chaired by our colleagues Fred Epstein and Zbenyk Pisa, analyzed by Jaako Tuomehieto, and reported by Hugh Tunstall-Pedoe. Several here were consultants.

The main null hypothesis for CHD (and separately for stroke) was that there was no relation of 10-year trends in serum cholesterol, blood pressure, and cigarette consumption to changes in 10-year incidence (fatal and non-fatal).

The second main null hypothesis for CHD was that there was no relation of 10-year trends in case-fatality rate (in 28 days) and 10-year trends in acute coronary care.

Much attention was given to standard measures of risk and disease and quality control, but we can all imagine the problems attendant on a study in X centers worldwide. The investigators are up-front about not all issues being measures in all centers, that new and recurrent attacks could be separated only in a few centers, that rates referred to the total population, not disease-free subjects, confined to ages 25-64, and varying frequency of a midway surveillance between 0 and 10 years.

Results: The data for the primary hypothesis showed a weak relation between trends in CHD and changes in risk factors, strengthened by building in the analysis a lagtime for the effect on disease rates of risk factor change. The trends of stroke were even less clearly related to changes in risk factors. The secondary hypothesis about the effect of acute care on case-fatality and mortality showed clearer positive effects.

MONICA reference:

CROSS-POPULATION TRIALS

Finland/Italian Diet Study

TELL THE STORY. Once I was told by Brozek when I commented on the weight gain he reported in men who stopped smoking, "The most popular of studies will be the ones that prove the obvious." Keys would have predicted within a couple % the results of the diet Italo-Finnish diet switch. It was wonderful that the obvious was done.

GEOGRAPHIC PATHOLOGY

The International Atherosclerosis Project was born early in CVD epi history in the minds of Henry McGill and Russell Holman, two of the types of pioneers I have described as comfortably embracing the clinic, in their case, dead patients, the laboratory, and contrasting cultures. As McGill put it: "knowledge derived by combing the methods of epidemiology, tissue pathology and clinicopathologic correlation." "... to measure the distribution of atherosclerosis in several human populations in order to relate the severity of the disease to environment, race, and clinical manifestations,." McGill, 1968

He saw clearly that he could get closer to correlations of the environment with fundamental mechanisms and pathology by direct examination of the arteries than fooling around with the clinical vagaries of the disease so poorly correlated with pathology or exposures.

This he believed would make up for the bias and unrepresentativeness in collections of autopsied people, if he were especially careful and consistent in his measurements and explored relationships repeatedly and in many and varied populations. Admitting the limitations of proof, they concluded, and our community has accepted that: ". . . because the results in [many and] various subsamples are consistent, and because many tests have been performed to identify and to reduce the effects of known sources of bias, we believe that the assumption is reasonable ." The community shares that conclusion.

CONTRIBUTIONS OF INTERNATIONAL COMPARISONS IN CONTRASTING CULTURES

Epidemiological investigations among contrasting cultures have:

- **addressed variations across a wide range of human characteristics and disease experience;**
- **validated large cultural differences in the prevalence, incidence, distribution, and mortality rates of the major cardiovascular diseases, including their near absence in some cultures;**
- **documented great differences in the average levels and distributions of the major CVD risk factors across human populations;**
- **established strong ecologic correlations of risk characteristics and population disease rates, including the major determinants of population differences;**
- **established the universality of the risk factor paradigm for causes of CVD within and across human communities, under different cultural conditions and absolute levels of risk;**
- **demonstrated culturally different proportions of the population burden of CVD attributable to major risk factors;**
- **confirmed the universal genetic evolutionary susceptibility of human populations to heart attack and stroke and their biological risk factors;**
- **shown different age trends across cultures, including examples of the absence of such trends in some cultures;**
- **validated changes over relatively short periods in the attack and death rates from heart attack and stroke, and in their risk factor distributions, in both directions, among populations in transition;**
- **established the primarily environmental and sociocultural origins of major epidemics as demonstrated in immigrants' rapid acquisition of the risk profile of the adopted culture;**
- **elucidated causal factors necessary for a significant population burden of CVD [diet and elevated blood lipids] and the contributing and multiple interactive risk**

characteristics causing variations in population CVD rates, thus prioritizing intervention strategies;

- helped establish the concept of “sick and well populations,” pointing to the pursuit of a combined, complementary medical and population-wide strategy to CVD prevention;
- helped establish that heart attack and stroke are preventable and not obligatory phenomena of aging;
- helped establish that elevated individual and population risk of CVD is preventable — in the first place.

THE FUTURE:

Just as contrasting cultures in Italy and Greece, and Japan and Finland, and within South Africa, taught us so much in the prehistory and early period of formal CVD prevention research, the wide variability of lifestyles, risk characteristics and disease rates of INTERSALT, INTERMAP, and INTERHEART Studies represent the promising contemporary scene. These studies have been bright and focused, quick and dirty, cheap and reliable, maximizing inter-individual and population variation and minimizing intra-individual variation of measurement. These approaches should flourish as new methods and biologic markers are found, including the more prevalent of candidate genes and alleles.

Similarly modern mass postal surveys have proved very effective research strategies. They are not readily adapted to cultural comparisons but might be tried.

The experimental strategy of trans-culture intervention is a clever way to confirm the obvious, such as returning the aborigines from reservations to their sacred lands and customs, and metabolically transforming groups of Finns into Italians!

More appropriate is the issue of survey, case-control, and cohort studies where now a great deal of importance lies in attempts to maximize the between-individual and between-population variability and minimize within-individual variability by the standardization of measurement and diagnosis.

We clearly need more such quick and dirty strategies with limited goals in the currently weakened environment for the support of large and long term epidemiological studies and trials.

ANECDOTES?