THE SEVEN COUNTRIES STUDY

A scientific adventure in cardiovascular disease epidemiology

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To Ancel Keys
on his 90th birthday

Preface

The fieldwork for the Seven Countries Study began in 1958. During the past 35 years a tremendous amount of work has been carried out in that study, under the leadership of Ancel Keys. Three monographs and a countless number of papers have been published. Nevertheless, there is no publication summarizing how the study developed in the different countries, nor are the major results of the study and their public health implications available in one place. Therefore the idea arose in connection with the international symposium, 'Lessons for Science from the Seven Countries Study' (held on October 30, 1993, in Fukuoka, Japan, organized by Professor H. Toshima), to assemble this history. An editorial committee was formed, consisting of Daan Kromhout, Alessandro Menotti, and Henry Blackburn and all principal investigators of the cohorts participated in this undertaking. Professor Frederick Epstein kindly provided a chapter on the public health implications of the study. All these made this document possible, from the personal perspectives of the investigators. This book provides an overview of a study that has greatly influenced science and the public health as well as our own careers. It would not have seen daylight without the administrative support of Anke Roccuzzo, Karin Bruineman and Nola Fortner. We gratefully acknowledge their contribution.

The Editors
December 1993

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The Principal Investigators acknowledge the gracious cooperation of the study communities, participants and field teams over the past 35 years as well as achievements of the coordinating centers:

Laboratory of Physiological Hygiene and Division of Epidemiology, University of Minnesota, School of Public Health, Minneapolis, Minnesota, U.S.A..

Laboratory of Epidemiology and Biostatistics, Istituto Superiore di Sanitá, Rome, Italy.

University of Leiden and the National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands.

All these played a crucial role in realizing the study.

The many sources of financial support that carried the Seven Countries Study through the entry examinations and the five and 10 years' follow-up surveys have been acknowledged in the 1967, 1970 and 1980 monographs. The 25-year mortality follow-up was realized mainly through local grants. The research of the 25- and 30-year follow-up data from Finland, Italy, and The Netherlands was partly made possible through a grant from the National Institute of Aging, Bethesda, U.S.A..

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Introduction

The Editors

The Seven Countries Study (SCS) has become a classic in science for its pioneering effort in cardiovascular disease (CVD) epidemiology and for its powerful lesson to science: that mass phenomena determine the population rates and the preventive strategies of CVD. The idea of the SCS arose in various forms in the minds of imaginative individuals capable of integrating laboratory, clinical, and population evidence. The study was given substance and direction by its leader, our colleague, Ancel Keys.

The SCS developed out of a rich set of observations made by a number of clinicians and investigators. It emerged in embryonic form in each of the seven countries. There was, in the late 1950s, a readiness for the ideas, along with preparedness for effective research among disciplines and across cultures. Ancel Keys and the Minnesota group, who had participated in physiological studies during and after World War II, had found the importance of nutrition and lifestyle in human biology (which they called physiological hygiene), and had recognized early that cardiovascular diseases were a major new public health concern. Keys and colleagues were also prepared with quantitative thinking and computational skills, able to link ideas, bridge disciplines, and apply methods appropriate to the scientific question. Taylor and colleagues at Minnesota in 1957 initiated U.S. efforts for the SCS in a study of CVD rates in railway occupations that required different levels of physical activity. At the same time, researchers in several parts of the world were examining similar issues: Karvonen and the Finnish group, Fidanza and Puddu of the Italian group, Buzina and Djordjević with the Croatian and Serbian groups, Aravanis and Dontas and the Greek group, Kimura and Toshima and the Japanese group, and Van Buchem and Dalderup and the Dutch group. Each had already begun explorations of population phenomena in CVD, testing hypotheses about the causal role of diet, physical activity, and lifestyle. Back in Minnesota, Keys, Grande, and Anderson also made crucial systematic metabolic experiments in the precise serum cholesterol effects of diet changes. Essential to the whole were the observations of Paul Dudley White and Noboru Kimura, who put into bold and simple terms the differences in CVD frequency and arterial pathology seen around the world. Meetings between all these remarkable people were stimulated by Ancel Keys; the ideas for collaborative research rapidly took hold, and active work began. Pilot studies with the Finns in 1956, and the Italians and Greeks in 1957, demonstrated feasibility of the SCS in the field. The central coordinating grant to Professor Keys from NIH allowed the definitive cohort surveys to begin in Croatia in 1958, while the U.S. Railroad Study had proceeded in 1957 under a separate grant to Henry Taylor.

Fortunately for the SCS, national Heart Foundations and other groups were ready to support the early phases of these activities. The U.S. Railroad Study profited from the support of the new National Heart Institute (NHI). Ancel Keys, of course, played the crucial role of putting all the ideas together in a clear proposal to the NHI for collaborative research among the seven countries. He had the international contacts, the vision, and the experience to move this major project forward.

Finally, the special experience and knowledge of each of the SCS principal investigators about their professional fields, and about the geography and culture of their lands, along with their clinical contacts and political clout, enabled the whole SCS operation to be put in motion. The central NIH budget at the time was only about $25,000 per year per center, so the fund raising talents of all the PIs were quickly developed!

Keys and collaborators hypothesized that differences in population rates of CVD, and individual risk within populations, were related to mode of life and risk factors, including composition of the diet. To examine this hypothesis, formal cross-sectional surveys were conducted, starting in 1958, among samples of men ages 40-59, in seven countries contrasting in composition of the diet and in purported heart disease rates: former Yugoslavia, Italy, Greece, The Netherlands, Finland, Japan and the U.S.A.. Baseline survey participants were entered into cohorts, and both the diseased and disease-free were followed for 30 years in most areas. The study was unique for its time, with 'adequately' sized 'chunk' samples in 16 areas as the cohorts, with standardized risk factor and disease measurements, training of teams, and central coding and analysis of data. The SCS became the prototypical population comparison study, made across a wide range of diet and disease experience.

As remarkable as these beginnings was the later emergence of leadership in the SCS from various places, where and when it was needed. Ancel Keys' leadership was essential to organize the study, prepare the initial collaborative proposal and, over the years, bring out the three major monographs: the 1967 Acta Medica Scandinavica Supplement, the 1970 Circulation Supplement, and the 1980 Harvard University Press Monograph. Each of these efforts was a *tour de force* which brought the diverse findings together in a way no other investigator or editorial board could have done as cogently and effectively. But other leadership appeared when the SCS came under its greatest threat; the central grant expired in the late 1960s, and soon after Dr. Keys retired, his base of operations was constrained. This was paralleled by the necessarily intense preoccupation in Minnesota with new activities to assure the survival and growth of the Laboratory of Physiological Hygiene, then and still, a largely self-supporting academic institution. Thus, in the late 1960s, much of the SCS energy, data collection, and coordinating responsibility was shifted to the capable hands of Alessandro Menotti and the Rome center. Since then, an important new axis of leadership has developed between the Netherlands, Rome, and Finland,

with a rich collegial sharing of ideas, initiatives and new data collection for new researches. The SCS owes much to the enterprise of Daan Kromhout, Alessandro Menotti, and Aulikki Nissinen in this development.

The SCS was first to make systematic comparisons of CVD rates and characteristics of risk in contrasting cultures. It was first to combine cross-sectional surveys with long-term follow-up among cohorts. It was first to compute population (ecologic) correlations between lifestyle and risk factors, and between risk factors and disease, and their *changes* over time. It was first to apply multivariate regression coefficients derived in one population to findings in men of the same age in another. In addition to these achievements, the study continues to redefine its mission and hypotheses. For example, there is every evidence of continued success in long-term follow-up of survival in the cohorts. Dr. Keys continues to study longevity related to characteristics at entry. And research by the several investigators moves forward to explain further the large differences in population CVD rates and the individual differences in risk, with respect to differences *and to changes over time* in diet, and other risk factors.

Of course, there are problems. The Seven Countries Study has a relatively small number of units to compare, with few degrees of freedom for the ecological correlations, and making these correlations at all was early criticized. Some have also criticized the selection of the different geographic areas, the varied occupational composition of the populations compared, and the obvious technical limitations of measurement and classification across areas by national teams, often under difficult field survey conditions. It is true that improvements have been made in the configuration of populations for such internal and international comparisons by random selection of greater numbers of units, etc. But the SCS was not only 'state-of-the-art' for its time, it was bold and foresighted in its concepts and thrust. And, as we increasingly realize today, the ecological associations of habitual diet, other risk factors, and population rates of disease, in themselves weak sources of causal inference, are, nevertheless, with strong congruent evidence from the laboratory and clinic, valuable indicators of the forces underlying mass diseases. When the evidence is consistent, the population correlations may indicate the *major* determinants of different population rates of disease.

This volume describes a great scientific adventure in cardiovascular disease epidemiology. All principal investigators wrote chapters about their contributions to the SCS from their personal perspectives. The resulting unique document describes the development of an international collaborative study which has greatly influenced thinking, practice, and policy in cardiovascular medicine and public health.

1

THE INCEPTION AND PILOT SURVEYS

A. Keys

The Seven Countries Study is the culmination of a prospective study started in Minnesota in 1947, long before there was any idea of an international study, and 10 years before international field tests of methods in Nicotera in southern Italy, and then on the island of Crete. The actual start of the study was in Makarska in Croatia, then a peaceful part of Yugoslavia.

The end of World War II meant release from war-related work; time to think and plan new research. The news in the American public press was no longer only about the war and its political and economic aftermath. Among reports of new events were increasing notices of executives dying from heart attacks. We could speculate about the epidemic of coronary heart disease and its cause. Middle-aged men, seemingly healthy, were dropping dead. There was talk of the stress of being an executive. But what was the difference between those attacked and those who stayed well?

The Basic Idea - The First Prospective Study

Suppose we examined middle-aged executive men, measuring and recording characteristics that would identify them in regard to items conceivably associated with susceptibility to coronary heart disease. If the examinations were repeated annually and vital status checked over the years, eventually some of the men would have heart attacks while others would stay well. Comparison of the entry characteristics of the coronary victims with those of the men who stayed well would reveal what years later would be called risk factors. With such knowledge we could warn men about their risk and try to alter the risk factors.

Here was the challenge to the staff of the Laboratory of Physiological Hygiene at the University of Minnesota. We had no idea of the number of men to study or the length of time needed to distinguish, statistically, coronary victims and their fellows remaining healthy. In planning such a prospective study it was necessary to take account of facilities, staff, and costs. A plan was drawn up and, with agreement of the School of Public Health of the University, a request for a grant was submitted to

the U.S. Public Health Service. As it turned out, the plan was too limited, and the request for a grant too modest. The request was promptly approved.

The idea appealed so much to the Public Health Service that it quickly followed suit, organizing and financing the same kind of prospective study on a much bigger scale. The study was to be operated by a committee with Dr. Roy Dawber as chairman. Thus was born the Framingham Study.

Plans for the study in Minneapolis were made in 1946. The subjects, executive men aged 45 to 55 in Minneapolis and St. Paul, were recruited, and their entry examinations, started in 1947, were completed in February, 1948. The study was called the CVD Study, short for cardiovascular disease. The re-examinations in 1949 and 1950 were satisfactorily made with the able assistance of Doctors Henry L. Taylor, Austin Henschel, and Ernst Simonson, all now deceased, the clinicians being Doctors Rafael Carmena and Carleton Chapman. They were followed by Dr. Henry Blackburn who became the permanent member of the staff in charge of clinical work.

A Year at Oxford, Visiting Professor in Magdalen College

In 1951, I was able to take sabbatical leave and go to Oxford University for a year as visiting professor in Magdalen College. In that year, I was called to Rome to be chairman of the first committee on food and nutrition of the Food and Agriculture Organization (FAO) of the United Nations. At the meeting all the discussion was about undernutrition in the un-developed countries. When I asked about the problem of diet and coronary heart disease no one was interested. Dr. Gino Bergami, Professor of Physiology at the University of Naples Medical School, said coronary heart disease was no problem in Naples.

Back in Oxford I made obligatory visits to colleagues and medical schools in Aberdeen and Glasgow in early 1952 and was free for a time. It was cold in Oxford, we were tired of food rationing and I remembered Bergami's claim. When I asked him about it he said, 'Come and see.' It was a welcome invitation.

Margaret and I loaded our little Hillman automobile with apparatus for measuring serum cholesterol and headed for Naples. In Naples we found Bergami was right about the general population's freedom from coronary heart disease, but there were patients with myocardial infarction in private hospitals catering to rich people. The diet of the general population was obviously very low in meat and dairy products, and Margaret found very low serum cholesterol levels in several hundred workmen and clerks brought in for examination by Dr. Flaminio Fidanza, an assistant to Bergami in the Physiology Department.

I was taken to dine with members of the Rotary Club. The pasta was loaded with meat sauce and everyone added heaps of parmesan cheese. Roast beef was the main

course. Dessert was a choice of ice cream or rich pastry. I persuaded a few of the diners to come for examination, and Margaret found their cholesterol levels were much higher than in the workmen (Arch Intern Med 1954; 94: 328). A few months later we went to Madrid as guests of Professor Jimenez Diaz, the foremost cardiologist in Spain, and found a similar picture in a poor area of Madrid (Metabolism 1954; 3: 195). Professor Diaz was a genial host but scoffed when I suggested that heart attacks might be related to the diet. Dr. Francisco Grande Covian organized all the work in Madrid and made sure we enjoyed our stay in that great city. Paco, as everyone called him, was unhappy with his position in the Medical School and before long he joined the staff of the Laboratory of Physiological Hygiene. He remained as a major collaborator for 20 years before returning to Spain.

Telling the Story in Amsterdam and New York

Shortly after the survey in Spain I was invited to speak at a joint session in Amsterdam of two international congresses, one on diabetes, the other on nutrition. I told about the surveys in Naples and Madrid and suggested that there could be a sequence - fatty diet, raised serum cholesterol, atherosclerosis, myocardial infarction. Almost no one in the big audience took me seriously. The sponsors of the Amsterdam Congresses gave my lecture to Voeding, the local journal on food and nutrition, which promptly published it (Voeding 1952; 13:539-555). Voeding is a respectable journal with very little circulation outside the Netherlands and even there primarily read by nutritionists. Not surprisingly, the lecture had no international attention. Years later I made some photocopies for colleagues because they had never heard of it. A few months after Amsterdam I gave the same lecture at Mount Sinai Hospital in New York. The audience was very small, but one of the listeners was excited by the thesis on the relation of the diet to coronary heart disease. That was Dr. Frederick Epstein. When some other reports seemed to be in harmony, he became extraordinarily effective in spreading the message all over the world.

Different Populations

The crude surveys in Naples and Madrid convinced us that surveys of men in different populations would be revealing. In 1954, I organized a meeting in Naples of prominent investigators from several countries to discuss the coronary problem. Hakvin Malmros from Sweden told about the disappearance of coronary heart disease in populations whose food was greatly reduced by the German occupation in World War II. He had reported it in 1950 in Acta Medica Scandinavica 1950; Supplement 246: 137. Vartiainen and Kanerva in Finland had written about atherosclerosis and wartime in 1947 (Ann Med Inter Fenn 1947;36:748). The connection

between nutrition and mortality from coronary heart disease during and after World War II was reviewed by Schornagel (Docum Med Geogr Trop, Amsterdam 1953;5:173).

The major change in the food supply in wartime had been a great reduction in meat and dairy products. In hindsight, food calories were reduced, but more significantly there had been a drastic reduction in saturated fatty acids in the diet. No one at the meeting in Naples came up with another inference that could be suggested. Undoubtedly many of the older members of the starving populations had well-developed atherosclerosis before the diet change. Why did some of them not have heart attacks? Certainly the diet change must have caused a great decrease in the cholesterol level in the blood serum, so there could have been a decrease or cessation of further enlargement of the atheromata. But would that alone have prevented heart attacks? Could it be that atheromas in the coronaries were reduced by the drastic change in the diet? In recent years it has been reported that this is possible with a drastic change in the diet, but there is controversy about it.

At the Naples meeting all agreed that comparable prospective studies in different populations could discover common characteristics associated with susceptibility to coronary disease. The problem was how to organize, finance, and carry out such comparable studies in different populations. In the meantime surveys would be useful.

International Surveys

The most prominent participant at the Naples meeting was Dr. Paul White, President Eisenhower's physician, who would thereafter be with us in visits all over the world, discussing and surveying the coronary problem. All doors of medical schools and hospitals were open to him, Margaret and I trailing along taking measurements, including serum cholesterol, on samples of men in the populations.

Those travels found great differences in the frequency of hospitalized coronary heart disease, in the mode of life, including the diet, and in serum cholesterol levels. Professor Jack Brock, head of the Department of Medicine at the University of Cape Town Medical School, invited us to look at the situation in Cape Town. On the way to Cape Town we stopped in Uganda where Dr. Jack Davies, pathologist in Kampala for the region, had made preparations to entertain and instruct us. He had arranged a display of 200 hearts dissected with the coronary arteries opened. In all but two of the hearts were the coronaries essentially clean, but those two had extensive atheromata. He explained that those were the hearts of butchers whose pay for their work was the offal, the entrails, which formed a part of their diets.

In Cape Town the excellent Groote Schuur Hospital has two wings, one for 'Europeans', as white people are called there, the other for all other patients -

Blacks, East Indians and mixed groups called 'Cape colored'. The medical staff, all trained in England, served both wings equally. There was discrimination in admission to the hospital but, so far as we could see, not in the quality of diagnosis and treatment. In the wing for Europeans coronary patients were common but perhaps somewhat fewer than would be seen in Minnesota hospitals. In the other wing of the hospital coronary patients were said to be extremely rare. Some of the findings in Cape Town were reported in The Lancet 1955;2:1103.

We made no cholesterol measurements or diet surveys but in a month of eating in private homes and restaurants the diets of the Europeans seemed to be primarily English, with local modifications reflecting the mild climate. In contrast, the markets and eating places for the Blacks indicated very little consumption of meat and dairy products. There was one curiosity. We saw lobsters in the common markets but never were served lobsters to eat. We asked why, and were told only the blacks eat lobster! We were puzzled, especially when we learned that some lobsters were shipped to Europe.

Surveys in Italy

A few days after returning from Cape Town we were off to Sardinia to make a survey in Cagliari. Our host, Professor Aresu, arranged everything for our convenience, finding a good place for Margaret to measure cholesterol, getting helpers to bring men for examination, escorting Dr. Paul White and Dr. Reuben Berman, cardiologist from Minneapolis, on tours of the hospitals. Paul and Reuben saw some heart patients but very few of them were of coronary origin. Margaret found the serum cholesterol level very low, and some doctors remarked that was surprising in view of the fact that eggs were abundant, and the men were eating an egg or two every day. They knew that egg yolks are full of cholesterol but they did not know that in man, in contrast to rabbits, dietary cholesterol in ordinary diets has relatively little effect on the serum cholesterol (Arch Inter Med 1950; 86: 189). Controlled experiments on man found little or no effect on the serum from adding cholesterol to diets containing the usual amounts of cholesterol in ordinary diets (Science 1950; 112: 79, J Nutrition 1056; 59: 30). Later studies found a small relation between serum cholesterol and cholesterol in the diet (J Nutrition 1960; 71: 61, J Lab Clin Med 1961; 57: 331). More evidence on the subject was reported in J Nutrition 1953; 87: 52 and 1965; 67: 52. Considering the findings in controlled experiments, the findings in Cagliari were not exceptional. It was gratifying to note that a population survey can agree with controlled dietary experiments.

From Cagliari we went to Bologna and found an entirely different picture. In Italy, Bologna is called 'la grassa', meaning it is the fat city and the most cursory inspection showed the appellation is justified. Not only was the diet fatty, people

tended to be fat. We examined the men in the Fire Department. The average Body Mass Index was higher than that of the men we had been studying in Minnesota. We could not blame it all on the diet; how much exercise do firemen have in a city where everything is built with stone? The serum cholesterol levels in Bologna were much higher than Margaret had recorded in Cagliari. Meanwhile, Paul White found no lack of coronary patients in the hospitals of Bologna and nearby Modena where the mode of life was similar.

What about the Japanese?

The vital statistics for Japan showed extremely few deaths attributed to coronary heart disease. In Cape Town the comparison was between two different races with a great difference in economic level. More relevant would be a comparison of men of a single non-white race differing in mode of life. Dr. Paul White joined us when we made surveys of Japanese men in Hawaii and Japan. At the excellent Kuakini Japanese hospital in Honolulu the doctors told Dr. White they occasionally had coronary patients. The serum cholesterol levels in samples of healthy Japanese men brought in for examination were rather low but not extremely so.

We found a different picture in Japan. Dr. Noboru Kimura, Professor of Medicine at the Kurume Medical School, had farmers in nearby Tanushimaru brought in for us to examine. Their serum cholesterol levels were extremely low. We could not properly survey their diets at that time, but, clearly, they were almost fat-free, no dairy products of any kind, almost no meat; the only animal foods were from the sea. In Fukuoka, the nearest large city, the diets and serum cholesterol levels were like those in Kurume, and the doctors were unable to find a coronary patient for Paul White to examine. The pathologist in Fukuoka told us about a great rarity he had found in the previous year. A Japanese doctor who had returned to Japan after practicing in Hawaii for 20 years had dropped dead; his coronary arteries were atheromatous.

In Los Angeles the Japanese men were largely Americanized in their way of life, including the diet. Their serum cholesterol values tended to be only a little lower than the average for white men in Minnesota. At the hospitals we were told that Japanese men with myocardial infarction were not rare. The findings on the Japanese men in these surveys were reported in the Annals of Internal Medicine 1958;. 48: 83. A dietary experiment on Japanese coal miners in southern Japan found their serum cholesterol response to a change in the diet was not different from that expected from diet experiments in Minnesota. (Am J Clin Nutr 1957; 5: 245). Several miners could not finish the experiment; more fat in the diet than in their ordinary diet made them sick.

Ilomantsi and Surveys in Finland

A major stimulus to work on the coronary problem in populations was a visit to Ilomantsi, a large village in Karelia in the most eastern area of Finland, only a few kilometers from the Russian border. Martti Karvonen said it was reputed beset with coronary heart disease, and he took me there to see. There was no hospital but a kind of lazarette with beds for six men. One man was very ill with emphysema, another had pneumonia, a third was a young man who had been bitten by a bear; three men suffered from myocardial infarction. We went to a logging camp so close to the Russian border we could hear sounds from Russia. We enjoyed a sauna with the loggers and when we came out there were refreshments. The loggers had slabs of cheese the size of a slice of bread on which they smeared butter; they washed it down with beer. It was an object lesson for the coronary problem.

In 1956 Martti Karvonen organized surveys on men in east and west Finland and in Helsinki. The 24-year follow-up found 345 men alive, 152 dead. The habit of smoking cigarettes was the major risk factor for cardiovascular and all-causes deaths. The data were reported in the International Journal of Epidemiology 1984; 13: 428. The Body Mass Index at entry was higher in the survivors than in the men who died. The level of HDL (alpha lipoprotein) cholesterol in the serum at entry did not distinguish the survivors from the dead. Epidemiologists could object that the men were not random samples of populations.

Prospective Studies in Different Populations

All of the studies described above had faults. The men we examined were not random samples of populations, and there was a lack of proper controls and numbers. Prospective studies in different populations were needed. It was decided that the men to be studied prospectively should be relatively stable in lifestyle to reduce the problem of evaluating effects of changes. In this respect men in villages would be preferred to men in cities who too often change their ways and place of residence. Besides focusing on villages, we felt men long employed by railroad companies would be suitable for a long-time prospective study, because both in the United States and in Italy they seldom seek other employment. When they retire they receive a good pension and when they die the heirs have a death benefit certified by an official death certificate. The findings in prospective studies on railroad men in the United States and in Italy are summarized in another section of this history of the Seven Countries Study.

Prospective Studies in Villages

We wanted to make prospective studies on men in villages, but the first requirement was to put together international teams for working in villages. Methods and procedures must be tested and established. A trial in a village was needed. For this, Dr. Alfonso Del Vecchio, an associate of Dr. Fidanza in Naples, suggested his native village, Nicotera in southern Italy. There was no housing for a team in Nicotera, but not far away in Gioia Tauro there was a new Jolly Hotel and restaurant suitable for living quarters for the team.

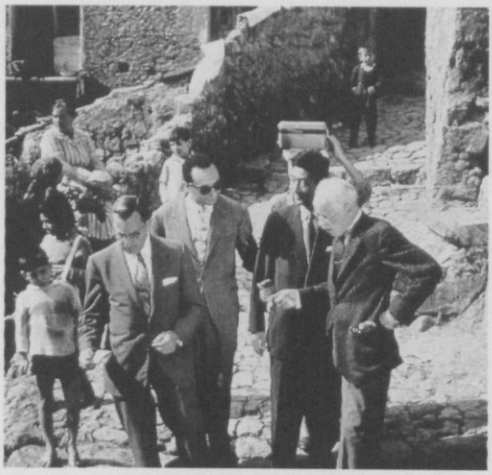
The doctors and officials in Nicotera were delighted about having an international group work in their village. They did everything to help, providing quarters for the work and getting assistants to round up men for us to examine. Soon we were busy with examinations. For serum cholesterol measurements we took advantage of a fact found by Dr. Joseph Anderson in Minneapolis. The cholesterol in blood serum dried on filter paper is stable for months if kept away from heat and light. Blood serum put on filter paper with a calibrated micro-syringe and dried in room air can be extracted and the cholesterol measured with a method adapted for micro-amounts. (Clinical Chemistry 1956; 2: 145). Great for working in the field without fancy apparatus!

Dr. Anderson reported his cholesterol measurements to us but said in a few samples the amount was unbelievably high. Some detective work found the explanation. Our work room had no window screens and there were flies. We discovered that fly specks contain cholesterol or something that acts like it in the analysis! Putting screens on the windows was the cure.

One day there was a terrific thunder storm, much lightning and high winds. While we were covering in our workplace a car drove up and a woman under an umbrella came to the door. She introduced herself as Dr. Louise Dalderup, sent by Dr. Muntendam, Secretary of State for Public Health in the Netherlands, to inspect our work. The outcome, several years later, was the establishment of the Seven Countries' cohort of men in Zutphen, a town in the central-east part of the Netherlands.

I wanted to find something about the mortality in Nicotera, and was given access to the official death certificates. In checking the certificates for the two previous years, I could not understand six records of men for whom death was attributed to 'gelosia', jealousy in English. I asked the local doctor to explain. He thought a bit and said it could be called lead poisoning. I quickly caught on; bullets are made of lead. Amusing, but enough to convince us that the local death records needed special explanations for epidemiological purposes.

Pilot survey in Nicotera, Italy, 1957.



A Trial of Working Men in Greek Villages - Crete

The experience of working in Nicotera showed that an international team could make a good survey in a village in Italy. The next question was to see if similar work could be done readily in villages in other countries. Dr. Andy Dontas in Athens was privy to our work and proposed we try to do the same kind of survey on the island of Crete. He, and Dr. Christ Aravanis, a leading cardiologist in Athens, made arrangements for similar work in villages on Crete with headquarters in Heraklion, the main port and largest city in Crete.

In October 1957 we loaded our station wagon in Rome for the work in Crete and had dinner with Dr. Vittorio Puddu, the famous cardiologist, in his apartment in a quiet area of Rome. Returning to the car we found a box of paper for the electrocardiograph machine we had lashed on top of the car was gone. Nothing could be done about it because we had to leave in the morning on a tight schedule. At Vibo Valentia we stayed overnight before taking the ferry to Sicily, where we would board the ship bound for Athens.

In Athens we left our daughter, Martha, with Jenny Dontas, sent our station wagon by ship, and took a 'plane' to Heraklion, where we set up headquarters in the recently completed Hotel Astir. We were truly an international team. Besides Margaret and I, and the Greeks, including Dr. Constantine Chlouverakis and the nutritionist Helen Sdrin from Athens, we were joined by Dr. Flaminio Fidanza from Italy, Professor Noboru Kimura from Japan, and Dr. Martti Karvonen from Finland.

The shortage of paper for the electrocardiograph machine was a problem. Jenny Dontas brought Martha to Heraklion for a visit. She helped her mother cut the paper lengthwise, doubling the length. The sensitivity of the machine was reduced, so we could get the whole record on the half-sized paper.

The work went well in the six designated villages in spite of very bad roads and the language problem. Only the Greeks could speak Greek, but we were fortunate in finding a local who spoke English. George Arniotakis was not only a translator, but he helped every stage of the work, including enlisting other helpers and repairing our automobile, the rear springs of which were broken by driving on the bad roads. No matching springs were available, so George had the broken springs replaced with truck springs. They lifted up the rear end of the car so the headlights pointed straight down. No matter; we did not have to drive at night.

But George could not rebuild the roads to the villages. To get to one of the villages I drove the car at a snail's pace while Margaret and Noboru walked ahead removing boulders on the road . I had to return to the States for a couple of weeks, so Margaret had to drive the car. The narrow road from Heraklion to some of our mountain villages had been carved out of the side of the mountains. Gravel for eventual road repair was deposited on the edge of the road, where there was a steep slope down. There were occasional places for passing, but coming down one late afternoon, Margaret encountered a string of buses going up in a stretch of road with no passing space. She had no choice but to drive up onto the gravel pile, where several men from the buses got out and held the car almost out of the way; only the gas cap was knocked off.

We could not measure serum cholesterol in Heraklion. The samples of blood serum were frozen and sent by air to Athens, where they were kept frozen until they could be packed to stay frozen until carried to Minneapolis for analysis in the

Arrival of pilot study group in Crete, Greece, 1957

laboratory at the University of Minnesota. The levels of cholesterol proved to be low but not strikingly so. Helen Sdrin, the nutritionist, reported diets more or less in keeping with the cholesterol levels, but she could not do a complete job. In one of the villages I told George to ask the farmers about breakfast, wondering if they were like most farmers in southern Italy, who eat no breakfast. Most of the Greek farmers said they ate nothing before going to work in the fields but some said they had a glass of olive oil.

In the Crete villages coronary heart disease was rare, and the men seemed to be long-lived. We were told about farmers still working at 100 years of age, but could not check the vital statistics with death records which were written by hand in Greek. The villages of Crete were candidates for a prospective study, and our experience there assured us that the real work of the Seven Countries Study could be done in villages like those. When we told Dr. Ratko Buzina in the University of Zagreb, in what was then Yugoslavia, about the way things went in Crete, he said, 'Fine!' and began making arrangements for the first examinations for the Seven Countries prospective studies in Makarska and Slavonia to start in 1958. What happened in 1958, and later in Makarska and Slavonia, is another part of the story of the Seven Countries Study, which will follow.

2

IMPRESSIONS FROM THE FIELD

H. Blackburn

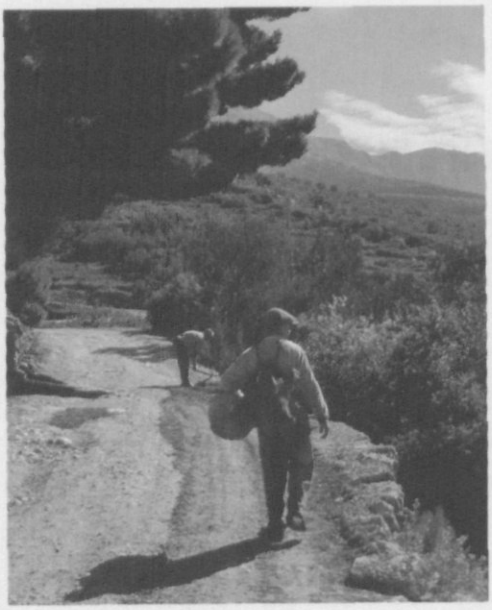
Fieldwork in the Seven Countries Study was a great adventure for all who participated, delightful and satisfying when schedules moved along well, or frustrating and threatening, requiring emergency corrective actions in days of failures and confusion. The following are excerpts from field journals depicting these extremes of experience and emotion while 'under fire.' Elsewhere, an extensive description is given about the details and 'color' of the field survey operations in each of the Seven Countries' areas for the baseline and 5-year follow-up surveys, compiled from vivid memories and journals kept in many of the areas. These anecdotes are available to any interested reader.[1]

Dalmatia, First Round, 1958

September 28th. 'We all rose early this morning to bid adieu to Paul Dudley White, after which we formally opened the Seven Countries Study in Makarska, on the Dalmatian coast of Croatia in Yugoslavia. We are situated in a virtual desert of crystalline limestone mountains that tower above the Adriatic, tiny vineyards scattered on their slopes. Shepherds are huddled here and there in the cold dawn as others move into the terraced olive groves. There is everywhere the tiresome, focused preoccupation of peoples in a land where soil and water are scarce. Our central headquarters, Hotel Jadran, is poised above the shimmering sea with a view of the archipelago through a haze on the horizon.

Day 1 in our first village, Tucepi, just south of Makarska. We had a five minute power failure at 1:00 p.m. that required a call to central power. They promised no further breaks! The technicians are new and inexperienced but full of good will. The clinicians are well trained, familiar with American nomenclature and diagnosis, and make thorough examinations while remaining on schedule. We excluded only two people from the exercise test today, one due to emphysema and one for hip disease.

[1] H.Blackburn, The Seven Countries Study: Adventures in the Field, Division of Epidemiology, School of Public Health, 1300 2nd St, Suite 300, University of Minnesota, Minneapolis, Minnesota 55454.



Dalmatian coastal road, 1958

The coastal road from Split south to Dubrovnik was apparently last redesigned and repaired under Napoleon! A couple of men in every village along the route are delegated full time to maintain the road, filling pot holes in the clay, scraping and smoothing and tamping. We learned that we can often transport our team from coastal village to village more effectively and comfortably by boat than by bus or jeep. Thus, we trundle generator and ECG machines and laboratory equipment aboard ship at the hotel dock, and accompany them to the next stop. Because of power variations and failures we use a generator, sometimes running all day, but placed as far away from the site as possible to reduce noise. Today an unanticipated hazard was an invasion by wasps! Our faithful driver, with a long cane pole and gasoline-soaked flare, saved us by smoking out their nest under the eaves. Another hazard required particular ingenuity. When the blood sample is centrifuged and serum separated, standard aliquots are pipetted onto spots of Watzman #2 filter paper, and these hung outdoors to dry. We had neither anticipated that fly specks would be deposited on the drying spots, nor that they would contain cholesterol! We therefore hired a local child to fan the drying serum to keep away the flies. The dried serum strips are then cut, two kept in the local laboratory and two placed in a glassine envelope, and sent airmail back to Memorial Stadium in Minnesota.

September 30th. Much of our equipment has not yet arrived, from which experience we will learn to carry, in future, all important supplies as personal baggage! The lovely Indian Summer changed abruptly today to a rare and furious thunderstorm. The sound of the crashing surf is prolonged by tons of water sucking back

through a myriad of pebbles on the beach. In the field, we agreed today on all diagnostic classifications with Professor Hahn of Zagreb, and our chief physician, Ivan Mohacek, theirs being perhaps more objective than ours for 'chronic non-rheumatic endocarditis'. We also agreed that all four cases of chest pain were not angina pectoris. Professor Fidanza suggests that comparisons of coronary disease frequency made between samples in Dalmatia, Crete, Italy, and Finland may be inappropriate because the make-up of the communities is so different, a larger proportion of upper socioeconomic classes being found in some Seven Countries' areas than in others. We refer him and his observations to Ancel Keys for satisfaction!

October 1st. Since we have not yet received our U.S. equipment and the precious Sanborn Electrode paste, we get terrible electrocardiographic records using home-made, brine-soaked pledgets. Our frustration in the examination room is assuaged only slightly by the magnificent view from our window in the Podgora Civic Center perched high above the sea. Our routine is interupted by people who constantly bring us 'moste' to drink at each day's stage of the new wine, along with fresh figs, grapes, and apples by the basketful. Constipation is no hazard in this land!

October 7th. Tonight the team conducted a seminar on arterial thrombosis and reviewed the theory that thrombus formation is a focus for organizing atheromas. We concluded 'that the very labile and dynamic factor of clotting may be highly important, as well as the slower cumulative process of atheroma; they may even be related, and factors of diet, emotion, and physical activity may influence both.' *(Eds. Not bad for a theory in October, 1958!)*

Due to terrible alternating current (AC) interference from defective internal wiring and nearby power lines, we converted to battery operation today, rotating between three direct current (DC) sources using a 12-volt capacitor vibrator giving a constant 60 cycles at maximal output, stepping it down with a transformer. Batteries are connected in parallel but their effective life is only half a day. Our ECG paper drives fail, due apparently to the fact that the paper rolls were compressed into oval shapes during travel and are acting as cams, putting undue stress on the motors! But the ECG operation has improved vastly since the final arrival of American electrode jelly!

Professor Ferber of Zagreb points out that there is a high intake of grains from breads in this region, with a recent shift from corn to wheat flour. The best local products with the greatest nutritional value are sold immediately through traveling salesmen to urban markets. Wives sell all the eggs because 'egg money' is traditionally theirs. It turns out that children on occasion steal eggs from under the chickens for money to buy sweets. Most of the milk is skimmed and fed to hogs. Vitamin and mineral intake is borderline; rickets is widespread in Dalmatia but much worse apparently in neighboring Bosnia. It appears that the Muslim men there may pay as much as 300,000 dinars for a wife and they apparently choose nutritional deficiency

over wife deficiency! Most of the meager 10% of fat in the diet here comes from lard, never butter. But clearly, we must carry out seasonal dietary surveys because of the remarkable seasonal variations in foods available.

Our backs take a tremendous jarring when we commute in the U.N. jeep on the narrow, winding, rocky road. That 'highway' becomes the central focus of our lives when we commute down the coast to new villages. It is, in fact, quite dangerous. One wheel off on the shoulder, or an unexpected encounter with a 'Dalmatian jeep' (donkey) would send our vehicle bounding, rock to rock, terrace to terrace, a long way down to the sea.

We are 300 cardiograms behind schedule in mounting due to a defective Hungarian stapler. Our thumbs are bruised and bleeding from operating this awful machine. We use Scotch tape to mount ECGs in an emergency and Dr. Keys has suggested that we cable Minnesota Mining's Mr. McKnight himself, as follows: 'Stuck for sticky stuff. Send 1 mile of 3/4' Scotch tape.' (It was fortunate we did not do this as all records tacked down with Scotch cellophane tape quickly became permanently blackened beneath the tape.)

October 8th. After 10 days of constant field operation, several of us took a day's break for a fishing trip with a local partisan leader. The morning was warm with a soft haze and the sea a flat calm as we pulled onto an island. There one of the fishermen cooked our breakfast of sardines and tuna, roasted over coals. After eating more than usually of the fish, I discovered a live ascarid wriggling just under the skin, abruptly terminating my fish eating! Apparently all the fish are infested. The fishermen seemed scornful of my meagre appetite, as well as inability to drink slivovica (plum brandy) early in the morning, and wondered about my elaborate protection against sunburn. We soft Americans have two strikes against us when we attempt to socialize with seasoned peasants and powerful partisans!

October 10th. Flaminio Fidanza left the field study today and all parted good friends. Some had become ill-humored at his incessant preoccupation with the quality of field operations at every station, including the medical clinic and ECG room! That sentiment dissolved last evening with Fidanza's departing speech, given in eloquent Italian, in which he showed the greatest respect for the leadership of Ancel Keys, for the general spirit of international cooperation of the Seven Countries Study, and for the scientific and social significance of our common research effort. When the power failed he finished his fine oration, dramatically, by candlelight.

For the dietary survey, Fidanza and Ferber had ground up foods purchased from the local market, and aliquots of meals collected in random households. They put all in the deep freeze for later analysis for total lipids, fatty acids, amino acids, nitrogen, and ash in thier labs and Minnesota. Flaminio was persistent in running down such items as spinach, sheep's milk, and turnips, which others said would be impossible to buy on the market.

Group of examiners at Makarska, Dalmatia, 1958.

October 15th. Finally, our survey routine is 'perfected'. The gasoline generator functions splendidly as a stable power source, and there is no hitch in the examination schedule, now running at 40 men a day. Tonight we had a long electrocardiographic mounting session with much pleasant banter (and less pleasant singing). Professor From-Hansen and wife from Denmark worked diligently as the professor sang bass and stapled records, both with great aptitude. We live in trepidation each time the stapling machine jams that it will never work again. One technician writes names and numbers on the records. Peter and Margaret Brozek arrange cards for mounting the resting and post-exercise records. Professor From-Hansen cuts the strips with great accuracy. Liliana and I form a strong team, arranging the ECG strips prior to stapling. It looks as if we will get the whole batch mounted and ready for shipment to Minnesota by the end of the week.

Dalj, Slavonia, October 20, 1958.

Chosen for a diet contrasting with Dalmatia, this is a region of drab farming villages having no center, strung out, one-house deep, along a 2-3 kilometer main street of pitted slippery clay. These non-towns are surrounded by vast plains reaching far into the mists of Slavonia and Hungary. Myriads of geese honk and huge black pigs snuffle along the road, grunting in dirty belches. The cattle, too, are immense. Here is every evidence of material richness amidst spiritual poverty. Houses are unkempt, the water filthy, hygiene wretched, the people obese and sodden, living in a constant downpour of rain externally and slivovica internally. These prosperous 'kulaks' avoided Stalin's genocide but guard an ingrained prejudice against orders of any sort, government of all sorts, and particularly against giving blood samples. The rumor going about is that following our dietary survey their local taxes will be increased. This may be a reason for our poor survey start in Dalj.

Today we 'broke our backs' with 43 participants seen. Remarkably, none was drunk. But disaster lurks every morning as we turn on the ECG machines. The

machine I recently carried all the way to Paris for repairs is still unstable. Careful calculations of the electrode paste and paper rolls available suggest that we will make it -- but barely.

October 24th. The fog is heavy today. The ruddy farmers and rustic wives in patched trousers, the mud and filth, screeching geese and grunting pigs and rattling wagons; all recall the coarse peasantry of Breughel paintings from the Middle Ages. On sunny days we have no participant response at all; simply no one shows! The nearby market fair has also reduced flow to a trickle of 27 participants, on average, a day.

On the positive side, we are blessed with marvelous ECG technicians here; Sabina and Velica are competent, hard-working, uncomplaining and, most important, non-singing! All the Dalmatian cardiograms are now mounted and we are plowing through initial coding at the rate of 40 an hour, mostly 'normal' records, as we apply our newly devised Minnesota Code.

October 28th. After all was said and done, we finished in Dalj with only one missing participant and identified there by electrocardiogram two myocardial infarct patients. We have had a wonderful time with Pentti Rautaharju from the Finnish team. He works meticulously on the electrocardiograms and will soon come to Minneapolis where we will complete and document the Minnesota ECG coding system. I am now leaving my part of the fieldwork supervision to Pentti, and departing from Yugoslavia with mixed feelings. I much enjoy the company of colleagues and staff, need more time to complete the clinical classifications, and want to see the first formal round of the Seven Countries Study surveys wound up 'tight'. On the other hand, a long period of dysentery has left me near collapse. Accompanied by a good nurse in a first-class railcar to Zagreb, restored by a little salty bullion, I am now en route by rail to Trieste, and find I have the strength to make it to Venice. There I can rest and recover within reach of medical colleagues and friends in Italy. From 'the pits' of Slavonia, working in an epidemic of alcoholism and shigellosis, residing in a filthy hotel, and suffering bone-shattering roads, mire, and misty cold, and gruelling hours of survey routine, it is a pleasant relief indeed to hear the rails clicking, leading to the north and west, and to imagine the lights of Italy, Austria, and Paris. I can even dream of a cold glass of fresh orange juice!

Crevalcore, Survey Round 1, March 1960

Chosen for diets contrasting with southern Italy we are into the 'tough stuff' already in this prosperous farming country north of Bologna. AC interference seems with us permanently, and there is no convenient other room in which to house the ECG operation. Two typical old anterior myocardial infarctions were already

observed in the first 100 participants, plus a case of malignant hypertension with retinal findings and one diabetic with capillary aneurysms. But the routine is well established and I can securely depart from the field, leaving these instructions for Doctors Mohacek and Tedesco:

- Seek perfect ECG technique at all times, with a minimum of AC interference and baseline wandering;
- Good records are the most important asset in rendering the readings and the measurements reliable and accurate;
- Transport all apparatus by train after secure packing;
- Please make comments on the Seven Countries clinical criteria before they are put in final form;
- Record the first blood pressure before taking the second, as a discipline for letting the mercury fall to zero;
- Between stations, please take all Elema electrodes to Milano and exchange them or have them replated;

Suggested pattern for Seven Countries morbidity and mortality surveillance:

1 *Mortality.* A physician should interview the participant's physician and/or family in each death case. Review records made during terminal illness; create a brief narrative account with clinical or pathological diagnosis of cause of death.
2 *Morbidity.* Use the same procedure, including a repeat examination of the survey ECG and urinalysis on those with suspect cardiovascular disease events. We will provide central criteria for classification of new events.
3 *Electrocardiograms.* Repeat ECGs on all those found with abnormalities, or technically unsatisfactory records.
4 *Urinalysis.* Repeat urinalysis on all those with dubious or positive findings.
5 *Blood cholesterol.* Consult Dr. Keys for quality control measures.
6 *ECG trouble-shooting checklist for erratic records.* Check skin resistance, contact, grounding, polarity, magnetic fields, tremors, transformer, and amplifier defects, and power failure.

March 22nd. The first Crevalcore survey round has settled into a smooth routine. The Italian team, less stoical than the Yugoslav, Dutch, Finnish, or Japanese teams, works together effectively, is quick to identify bottlenecks and resolve them, and responds well to the daily confusions of all sorts. The noonday break, traditional in Italy, becomes a pleasant part of the long work day, when we can visit Trattoria Julia, a 'hole in the wall' with tables for a dozen people and a tiny kitchen with open gas burners on which Julia prepares exquisite dishes, especially spinach lasagna. Unfortunately, I have 'three strikes against me' with Julia; I am American and non-communist, I speak little Italian, and am not possessed of a gigantic appetite like my Italian colleagues!

Greece, First Round, September 1960

The special knowledge of the Professors Aravanis and Dontas and their colleagues, students, families, and friends living on Corfu and Crete, provides the background for the major scientific question addressed here: What is the long-term effect among rural, active peasant populations of a relatively high fat diet composed of high monounsaturated and low saturated fatty acids? Any 'mystical, life-giving properties of olive oil' can also be tested stringently. The Greek Islands otherwise share a salubrious environment, gentle climate, and characteristic Mediterranean living pattern, a diet with only occasional meat and chicken, frequent fish and seafood, and traditional daily staples of grains, legumes, vegetables, and fruits.

The field team is highly compatible, 'very Greek', expressing deep affection for their homeland. They enjoy working with the dark Cretan pappas, exploring their salubrious diet and dignified, timeless lifestyles. We share with participants a lemonade or an ouzo in the local tavern and listen as they do, with appropriate skepticism, to the political rantings from Athens over the radio in the square.

There is minimal evidence of modern industrial society on this island. The men walk to their fields or ride bicycles; television is not a major influence. We see grain winnowed in stone circles high on the plateaus of Crete by the feet of men or by women in black, pulled on a wooden sled by donkeys. We experience the mystery of the arid, rock-strewn plateaus during the grain harvest and travel to high pastures in which men enjoy each other's stories and company and dance at midnight under the bright moonlight. We now know Zorba's madness. We too have felt the heart swell in this stark but serene environment. We are mesmerized by the buzzing of midday flies. The cicadas 'saw' away at frequencies that mount during the day and slack off in the cool of dusk. At dawn we enjoy the donkey's bray while the whippoorwill's and nightingale's calls are wafted to us as from afar. We are enchanted by the purple sky that melds into the violet sea, by the softly lapping surf and the dappled sunlight through the grape arbors, as we gather at tables during the long midday break. We are fascinated by the preoccupation everywhere with obtaining water in this arid land and by the lushness of tiny oases found here and there under the panoply of olives and grapes, and on the southern coast, of bananas. Everything is designed according to ancient principles to maximize the water supply and guard its runoff.

Finland, Second Round, September 1964

The Finns make long voyages by boat, bus, truck, car and often by bicycle to come for their Seven Countries 5-year examinations at the Soviet border guard station in Ilomantsi. One of the remarkable things about Finland is that the men are so physically fit, yet their arteries are so involved with atherosclerosis. We are here because

of evidence that they eat the world's most effective cholesterol-raising diet, high in butterfat! The language too is distinctive, having a staccato sound, full of vowels and bell-like from the tongue of our young technicians, clipped and swallowed by our medical colleagues, and a bearish growl from the mouths of our participants. All creates a pleasant background harmony in the field station.

Culturally-determined motivation and competitiveness differ in the SCS field operations. The Finn participants, for example, appear generally challenged by an exercise stress test, 'giving it their all'. These examinations are the more technologically advanced of all surveys to date. Pentti Rautaharju and Herman Wolf have developed systems for recording simultaneous multi-lead electrocardiograms and exercise cardiograms, phonocardiograms, chest displacement curves, pulse wave velocities, and pulmonary function, with the promise that these will eventually be integrated into a quantitative prediction of functional capacity and, it is hoped, of future disease risk. As an interested collaborator in such highly technical undertakings, perhaps I may be permitted to observe that the instrumentation seems perpetually obsolescent, new instruments always taking precedence over the recent old; new questions consistently displacing the old ones, and new recording modes used before old ones are thoroughly exploited or published. The epidemiological need for consistency, and comparability and stability of measurement, is often superseded by the drive of new ideas, new recording systems, and new technology! Nevertheless, I fully expect some years from now to have available small black boxes to tie to people in field surveys; instruments that will integrate respiration and heart beats, and electrocardiograms and pulse waves, and give continuous readouts and predictions, in reliable and rugged recording systems. Perhaps we can then move into a modern era of physiological data processing applied to whole populations! *(Eds. This 1960 dream is not yet realized!)*

Japan, Second Round, March 1968.

We have examined 100% of farmers in the township of Tanushimaru! Here is the world's lowest diet in saturated fatty acids! The major field problem here is the damp cold, and we do a lot of walking around the station to ensure that kerosene stoves are distributed, so that the men waiting for blood pressure measurements will not be exposed to cold stress. We needn't have worried. These men are well adapted to inclemency. Another 'hazard' is our catered lunches, arriving in lacquered boxes with little bamboo trays of highly colored, sundry unmentionable squares, rounds and triangles of fish paste, rice paste, cold clots of rice wrapped in dark paper thin, spinach-like seaweed, all sorts of briny fruit and vegetable pickles and semi-cooked mussels and shrimps. I manage to do away with the rice, using chop sticks clumsily, much to the amusement of Japanese colleagues, washing it

down with Kirin beer, sufficient to survive until dinner with sake, and tasty tempura or sukiyaki!

But there is another field hazard: the legendary Japanese earthquake! This morning we were hard at work in the little frame school house of Tanushimaru, counting pulses, taking blood pressures and supervising exercise tests made on the incredibly powerful Japanese men. The flimsy school partitions, tied together around large bamboo poles, were set on wooden floorboards, set, in turn, on wood pilings. Suddenly, I felt an attack of vertigo. Looking out the window, I noticed the stone memorial to the founder of the school, made of three large stones, undulating each on the other and dancing a tango, yet not falling. The school floors and walls, tied together loosely, creaked wildly. All motion of the examinations poised, the Westerners looking at each other in consternation, the Japanese calm at their posts. The undulations continued for a good 10 seconds, subsided, came again slightly and then were gone. The lightness of the school's construction was then explained. It would have crumbled and fallen upon us if it had been built of masonry. We then felt a 'rush' from the earthquake experience, on this, the earth's most tremulous island.

There is another social hazard in Japan, which I encountered with the kind local physician of Tanushimaru. On his visits to our examining stations, we learned of his sensitivity and intelligence, and understanding of what we were about, as well as sensing his devotion to the community. When he invited us to his home, I commented on its simple beauty and tradition. He must have seen my eyes rest momentarily on a particular lacquer before shifting to other lovely artifacts around his house. Imagine my chagrin when, on the train north to Tokyo, I opened the package he had put in my arms as we left the Tanushimaru station and found that very same lacquer, a deep Chinese red with emblazoned gilt dragons, even now to be found in a 'Japanese Corner' of my Minnesota home after 25 years. Imagine my greater chagrin when I learned later that the lacquer had been handed down to him from his great-grandparents. It is difficult to deal with such generosity -- or with the social debt that it incurs!'

This is only a sample of the labors and pleasures, and ardors and concerns, of many months in the field, and at the Seven Countries coordinating centers, in efforts to insure the effective collection and handling of data, as well as coordination and collegiality among the study's devoted investigators.

3

COORDINATION OF THE SEVEN COUNTRIES STUDY

H. Blackburn and A. Menotti

It was anticipated that this chapter would be constructed by the two of us entirely from mutual records and memories. However, as has often been the case in our long experience with Ancel Keys, his clear and concise language would render unprofitable our attempts at duplication. Thus, we quote Keys extensively from the 1967 Seven Countries Monograph in Acta Medica:

'The basic plan of the program from which data are reported here was to organize parallel studies on men aged 40 to 59 in areas differing in the diet or in the reputed incidence of heart disease, or both, but with areas so chosen that within each there would be relative homogeneity. A major feature of the entire program was the adoption of the rigidly standardized methods and criteria, common protocol, and battery of observations and tests, and central coordination. This would assure, so far as possible, complete comparability of the data collected. Further, to assure such comparability, arrangements were made for interchange of professional personnel among the teams working in the several areas, and for centralization of statistical and some analytical services. The extensive explorations prior to 1957 led to more systematic programs with a plan to follow up men examined for five or more years. It was agreed that a suitable age range would be 40 to 59, and that a series of population samples should be studied in parallel. Accordingly, new programs from which data are here reported, were started in 1957 with the railroad employees in the U.S., and in 1958 in Dalmatia and Slavonia, Yugoslavia. These were followed by the programs which began in two areas of Finland in 1959, and in 1960 in Crevalcore and at Montegiorgio in Italy, Zutphen in the Netherlands and again on Crete. In 1961, the sample in Corfu, Greece was examined. In 1962 another study was added, the village of Velika Krsna, 50 kilometers south of Belgrade, Yugoslavia. The sample of U.S. railroad employees was (re-)examined in the same summer. The program in Japan, not strictly comparable in all details, began in 1958, at the farming village of Tanushimaru and in 1960 at the fishing village of Ushibuka.' In 1962 the Rome railroad sample was examined as a counterpart of the U.S.A. railroad. In 1963 the Serbian cohort at Zrenjanin (Vojvodina) was added, con-

sisting of men working in a large agro-industrial cooperative. Finally, in early 1964 the sample of Belgrade professors became the last cohort enrolled.

'Members of the central organization (Professor Keys and Dr. Blackburn) worked closely with teams in each of the countries. During the period of the initial examination in each area the central organization provided help to the local organizations in the form of supplies, equipment, and professional personnel'.

Establishment of Rosters

'In the areas of work in Europe and Japan, official lists of residents, with birth dates, are locally available. However, such lists require careful scrutiny. Men who migrate away from the area are often long retained on the list of residents while newcomers, particularly from that same general region, may not be listed for years and, inevitably, there are clerical errors in names and dates, and delays in correcting for deaths. Parish church registers, and electoral and taxation lists provide additional data, but detailed local inquiry among responsible residents is essential.

Initial official resident rolls are corrected for emigration and additions for the formation of a true roster of the eligible sample. Non-respondents are characterized as being in hospital, disabled, not in the area but reputed to be healthy, refused, apparently healthy, or refused with possible heart disease. Accordingly, there were 13 'chunk' samples of all men of specified age in the defined areas.

Among the total of 9,564 eligible men, 9,170 were examined in full, the coverage being 95.9%. It is notable that the coverage was nearly perfect in the rural areas, less satisfactory in the small town of Zutphen, and considerably poorer among the railroad employees'.

Examination Procedure

'Great efforts were made to assure comparability of methods and procedure on several sites. The locally responsible team was aided in the field by professional experts from the teams in other countries. Electrocardiograms were independently classified [centrally in Minnesota] by two or more electrocardiographers, at least one of whom was from another country. After the roster was established, a schedule of examinations was adopted and headquarters were organized, both for the examination and for housing the team of investigators and assistants. In each area local assistants made appointments for the subjects and then reminded or escorted them on the appointed day, so as to assure attendance at the examination centers. Transportation was provided when needed. Efforts were made to prevent the men from indulging in heavy exercise or heavy meals beforehand. While waiting, smoking was not allowed.'

The field survey procedure was as follows: *a* registration; *b* anthropometry; *c* medical history and physical examination; *d* electrocardiogram and exercise electrocardiogram; *e* urine sample; *f* respiratory test; *g* exit interview.

Classifications

Forms and codes developed centrally in Minnesota for common use in these collaborative studies cover demographics, medical history, physical examination, parental mortality, family status, smoking habits, and anthropometry.

'Serum samples from all areas were analyzed for cholesterol in the coordinating center at the University of Minnesota. Dr. Joseph T. Anderson directed the analytical laboratory and Nedra Foster supervised the technicians. All of the electrocardiographic tracings were independently read by at least two internists with special experience in electrocardiography. Dr. Henry Blackburn supervised the readings by the collaborating physicians and reconciled disagreements in classification. Dr. Joseph Brozek developed and standardized the anthropometric methods. Drs. J. K. Kihlberg, R. Willis Parlin and Norris Schultz of the University of Minnesota were responsible for the statistical work on the data from all the areas.'

Fieldwork

'Selection of the period for fieldwork in a given area required consideration of the seasonal activity of the subjects, as well as that of the proposed staff and, in general, this means concentration of examinations in a period not over one month. Before the fieldwork proper begins, the final roster of subjects must be established, local headquarters arranged, suitable local assistants engaged, and provision made for local transportation of both subjects and staff.

In general, it was found to be efficient to organize schedule and staff so as to 'process' from 150 to 200 men per week for 6 to 8 weeks; this required making effective arrangements to have the subjects available on schedule. It proved to be suitable to concentrate the examinations in the morning, leaving the afternoons free for 'book work', ECG classification, working up blood samples, etc., plus handling a few stragglers that could not be examined in the mornings. The clinician's schedule had to allow for the fact that in many areas it is impossible to avoid some demands for medical advice, particularly for local women and children.'

Such a program for cardiovascular field surveys requires a staff as follows:

1 director of field operations;
1 electrocardiographer;
1 anthropometrist;
2 internists who take histories and make physical examinations;
1 or more clinical consultants;

1 physician or physiologist to conduct respiratory tests;
2 assistants for electrocardiographic recording;
1 driver;
1 dishwasher;
1 biochemist or chemical technologist;
1 registrar;
4 helpers;
1 catcher to bring in subjects and run errands;
1 general helper.

'Every effort should be made to assure that the relationship with the subjects is developed from the start on a warm and personally sympathetic basis. The subject may seem to be only a serial number on the roster and appointment schedule, but he must never be treated that way. Ideally, a brief note about the findings on each man is provided to the local physician or public health nurse, not to the subject himself. When it is not feasible, each subject should be given a few words of reassurance at the end of the examination. When medical care is really needed, efforts must be made to provide this through local sources.

The experience of the teams in the field in Europe and Japan quickly made convinced internationalists of most staff members. Political arguments were avoided, and concentration was on the professional and purely individual human aspect of the work and life together; the result was a development of true friendships among staff workers of all nationalities and the most cordial cooperation of the subjects, their families, and the local officials. Though the subjects frequently had little comprehension of what the work was all about, the good will on both sides was readily apparent; it was often a problem to escape too much local hospitality in the villages. In general, the response of the populations to the appeal to participate in such surveys seems to be inversely proportional to the size of the community; the response is better in villages than in towns, and better in towns than in cities.'

Forms and Procedures

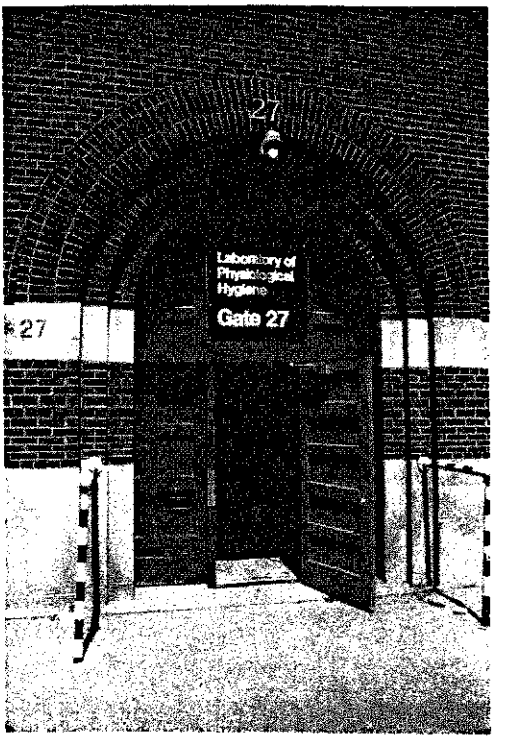
All forms and procedures were developed centrally in the Laboratory of Physiological Hygiene and tested extensively in the field in 1957, in the U.S. Railroad Study, and in the Nicotera and Crete field trials. We were considerably influenced in devising these forms and procedures by the principles of classification proposed by Moriyama (Journal of Clinical Diseases 1960;11:462):

1 The categories of a classification should be mutually exclusive and clearly defined;
2 the rubrics or categories under the various items should be related to the item and meaningful in terms of their eventual use;
3 the categories must be selected in such a way that the data within each sub-class are relatively homogeneous;

4 provision should be made for the classification of every case;
5 a reasonable frequency distribution should be obtainable from a good classification system;
6 the finer the classification the more specific will be the data; and
7 all classifications and editing procedures should be clearly specified in writing. Nothing should be trusted to memory.

It was also clear to us that a classification can only be as good as the quality of the observations on which it is based. These should be as objective as possible and based upon distributions of values obtained from well-defined normal and abnormal groups. Moreover, clinical disease classification for wide application cannot require radical departure from common diagnostic methods, and one axis of classification cannot be expected to be applicable to all purposes. All classes must be coded in binary or decimal form. Finally, there should be some basis for optimism concerning acceptance by authoritative medical bodies before attempting to promulgate a classification system throughout the wider medical public.

Coordinating Center, Stadium Gate 27.



Training

In almost every instance the Principal Investigator, or coordinators from each overseas team of the Seven Countries Study, visited the central Laboratory of Physiological Hygiene in Minnesota for a period of orientation to field procedures. For the first round surveys we, or someone we had trained, supervised the operation and data collection for all areas. On field sites, in the days just prior to initiation of surveys, regular staff review sessions were held on the use of forms and on procedures for interviews, anthropometric measurements, history and physical examinations, electrocardiographic and respiratory function testing, as well as urine and blood sample collection and processing.

One of us, or one of the centrally trained colleagues, circulated among examination stations as quality control officers, reporting needed adjustments in procedure and technique at regularly scheduled field staff gatherings. Quality control in the field also involved systematic editing of forms for gross errors, deficiencies, and omissions that could be corrected on site, as well as mounting and inspection of electrocardiographic and other technical records.

In most circumstances, for most items, duplicate forms and records and samples were collected both for safety and for the independent use of the regional teams for their own researches. The duplicates or aliquots were then forwarded by standard shipping practices, registered and insured, to Stadium Gate 27, University of Minnesota. There a statistician, and trained clerks received the records, labelled and entered them into appropriate files, and systematically edited the forms for errors and completeness. The field supervisor or Principal Investigator was notified in case of serious deficiencies, which were corrected by re-examinations in the field.

Clinical classification of findings at entry examination (prevalence coding) and for incidence cases was carried out in a detailed hierarchy, as described in the 1970 Seven Countries Study Monograph. This involves systematic application of criteria for combined data from the medical history and physical form, along with the electrocardiogram.

Adventures in Death Certification

A major central responsibility was standardized coding of causes of death, based on death certificates and medical histories, provided to the coordinating center by the responsible investigators.

In the 25-year follow-up experience, almost 6,000 deaths occurred in the 16 cohorts; about half the original participants. Because of the large variations in death rates, extremely high in Slavonia and East Finland, and low in Crete and the Belgrade professors, the preferences for one instead of another cause of death had to be examined carefully. Diagnoses and medical terms were frequently reported in

Latin in material coming from former Yugoslavia, reflecting the tradition of middle-European medical schools. Some knowledge of Greek helped in interpreting the Greek material.

The basically routine process of death coding provided personal insights for the reviewers on death as part of life, and on the destiny of individuals and whole populations. Some deaths were bizarre, others particularly tragic. For example,we recorded one death in an air crash (a Finnish farmer), 4 deaths due to lightning, and 4 from tetanus. An apparently late consequence of malnutrition and hardship during World War II was 119 cases of fatal tuberculosis, the majority in Slavonia and Velika Krsna of former Yugoslavia. Not a single tuberculosis case was recorded in the railroad cohorts of the U.S.A. and of Rome.

An indicator of the socio-cultural environment is provided by the suicide rate, highest in Slavonia, an agricultural area of inner Croatia, contrasting with no suicides in the Rome railroad employees, and only one in both Japanese cohorts! Suicide by firearms was preferred in the U.S.A. and Finland; hanging was used in the Mediterranean areas, with the exception of Crete where desperate people dove into a well! We recorded 7 homicides, 3 in Finland, 3 in former Yugoslavia, 1 in Rome and none in the U.S.A., Japan, Italy, or the Netherlands.

On-going Coordination and Analysis

In 1967 Alessandro Menotti took over in large part the coordination responsibilities then held by Henry Blackburn. Meanwhile, Menotti had completed a second period of formal training in epidemiology at the London School of Hygiene and Tropical Medicine and had participated in practically all the field activities held in the European areas from 1963 on. He had already started a long-term appointment as Research Associate at the Laboratory of Physiological Hygiene of the University of Minnesota. Our joint activities included training and testing field personnel in the

Preparation of the summary diskette by Bennie Bloemberg, Simona Giampaoli, Daan Kromhout and Alessandro Menotti, Rome, June 1990.

several measurement and clinical techniques, being present for all survey examinations, reviewing all clinical records for the final assignment of clinical diagnoses, and reviewing and coding all forms and death certificates, and descriptions for the final allocation of cause of death, following defined criteria. This work continued for the 15th anniversary examination in Finland (1974) and was extended to the associated study areas in Hungary, which were never fully incorporated into the Seven Countries Study, although they followed a similar protocol (starting late in 1965).

In 1973 Alessandro Menotti started scientific cooperation with the Istituto Superiore di Sanità in Rome (the National Public Health Institute of Italy), which involved access to the largest computer then available in Rome and to a group of physicists, mathematicians, statisticians, and computer people who, little by little, were 'converted' to epidemiological pursuits. This allowed relatively sophisticated analyses to be made on the Italian data and to full collaboration with the Seven Countries Study Group. For example, a large part of the analyses for the 10-year monograph and most subsequent analyses were performed in Rome. This was particularly useful after the University retirement of Ancel Keys in 1972 and the end of central funding for the study.

The role of the Rome center, crucial for coordination, became even greater when mortality data started to become available after the 10th anniversary surveys and when Menotti was appointed, in 1979, as research director for chronic diseases at the Laboratory of Epidemiology and Biostatistics of the Istituto Superiore di Sanità. In that laboratory, those who contributed to the central analyses were Gino Farchi, Arduino Verdecchia, Riccardo Capocaccia, Sergio Mariotti and Susanna Conti, from 1973 to 1984, and Fulvia Seccareccia and Mariapaola Lanti from 1984 on. Several original analytical approaches originated from this group, such as the concept of 'saturation effect' in multivariate prediction, the attempt to measure the proportion of the inter-cohort incidence or mortality differences explained by differences in risk factor distribution, and the use of risk factor changes over time in prediction of morbid or fatal events.

In 1979 came the official introduction of Daan Kromhout, then of the University of Leiden (and later of the National Institute of Public Health, Bilthoven, The Netherlands) to the Seven Countries Study Group, on occasion of the meeting of principal investigators held in September of that year in Heraklion, Crete. Soon after, a close cooperation started between Kromhout and Menotti, so that in a few years they shared all the coordination of the study group, with the major interest of Daan Kromhout in the nutritional aspects and of Alessandro Menotti in the risk factors. Between 1990 and 1991 they realized, with the help of collaborators in Bilthoven and in Rome, the summary tape, and then the disk, of the entire Seven Countries data, covering 25 years of follow-up for all areas. This has become the basis for 25-year data analyses used by all investigators.

4

STUDIES IN THE U.S. RAILROAD

H. Blackburn

The study of U.S. railroad men (USRR Study) was the 'baby' of Henry Longstreet Taylor, professor at the Laboratory of Physiological Hygiene (LPH) in Minnesota. He had the idea to compare coronary heart disease (CHD) rates among rail occupations to get at the causal role of habitual physical activity. Taylor realized that there would likely never be a 'definitive experiment', due to feasibility and cost, in which physical activity would be modified and the effect on heart attack rates measured.

Lewis Thomas once defined epidemiology as 'thumbing through death certificates', an insensitive and uninformed depiction, at best. But such a 'thumbing', done systematically and early on, revealed to Henry Taylor and those of us who had become his colleagues, that CHD death rate differences among rail-workers were in the direction of the hypothesis that physical inactivity is associated with higher rates. Taylor was also the first to criticize his own brainchild, pointing out, on the one hand, problems of misclassification of physical activity in the Railroad Retirement Board list of occupations, and, on the other, of selection bias which might concentrate workers who were ill, or becoming ill, among the less active railroad professions. This candid criticism of one's own offspring is perhaps less often found in science today. Taylor's basic integrity had been nurtured in a skeptical and dispassionate 'Old School Physiology' which put him in good stead for epidemiological pursuits.

To reduce these errors and biases the novel idea was proposed to NIH of examining the active and less active rail workers at their worksites, measuring incidence in the railway cohort while accounting for measured confounders and co-morbidity. To Taylor's surprise, and certainly to the surprise of some of his Minnesota colleagues, the proposal was approved by peer review in the National Heart Institute. Thus began the independent U.S. Railroad Study, which only later was coopted into the Seven Countries Study comparisons.

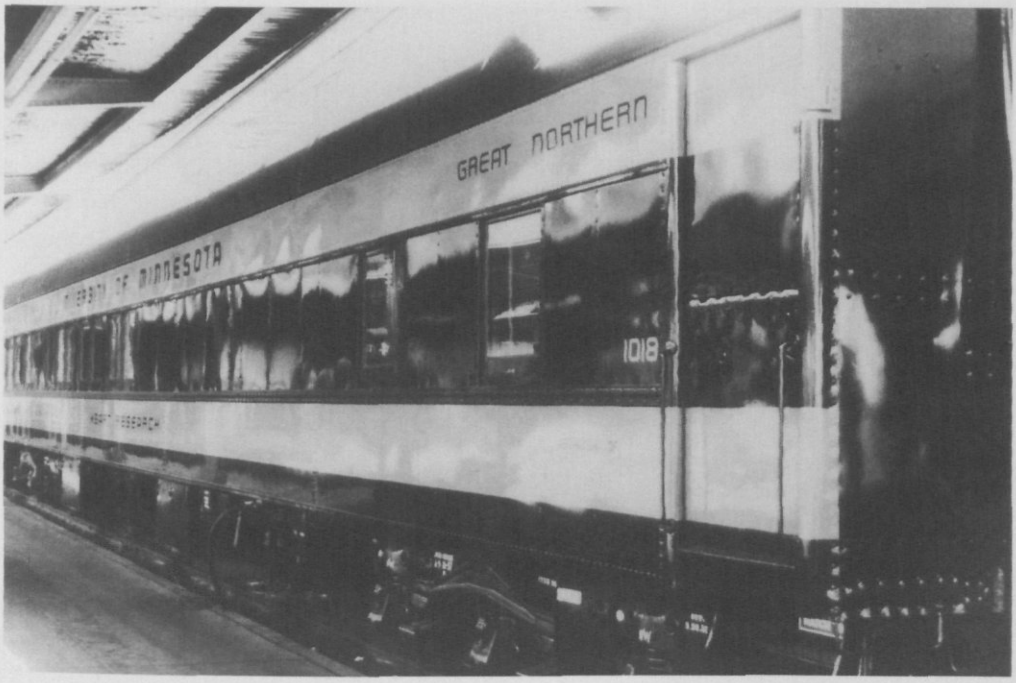
I first worked with Henry Taylor in 1954, as an LPH fellow, examining some 400 Minneapolis firemen in a tentative that failed for want of numbers or an adequate range of job activity, but that provided field experience which greatly strengthened

the subsequent proposal to study the USRR cohort. Early in these plans I was tapped to develop the 'instruments' and the diagnostic criteria for the rail study, which was to be put into the field formally in summer 1957, at about the time that Ancel Keys was to carry out pretests for overseas Seven Countries field surveys. Those surveys, to begin formally in the fall of 1958, needed comparable clinical-organizational efforts. Whether I was to be engaged immediately and directly with the USRR Study, or with the overseas Seven Countries plans, was a matter of debate between Keys and Taylor. I presume that Taylor won out because the railway activities were to begin a year earlier, and because both undertakings would profit from the earliest possible development and testing of examination methods, forms, and disease classifications for the USRR, with which I was deeply engaged after joining the regular LPH staff in 1956.

The USRR Study operation was 'first class' from the beginning, and one in which I was happy to be involved. I had a few pangs of regret when unable to accompany Ancel Keys in the fall of 1957 to conduct the pilot surveys in Finland, Nicotera in southern Italy, and Crete, but my services were urgently required to get the USRR show 'on the road'. This we did, with procedures, forms, and the beginnings of the CVD classifications, which would eventually include The Minnesota Code. In those exciting early days I enjoyed particularly working with Taylor in the design of a unique railcar traveling laboratory. He proved extremely skillful in face-to-face negotiations with rail management and union brotherhoods, obtaining, among other things, the long-term loan of a Pullman car. With the new NIH grant, he proceeded to have that car renovated in the Great Northern maintenance yards off Como Avenue in St. Paul (the site of the present-day Bandana Square Mall), where we spent countless hours supervising and kibitzing. The Laboratory car was well laid out, with a reception area, a series of examining rooms for anthropometric measurements, the medical history, and physical examinations and blood pressure, as well as a large work area for the resting and exercise electrocardiogram. Down the line was a booth for the chest x-ray and then a 'wet lab.' for the blood and urine sample processing.

After a trial run in the old St. Paul Depot, we moved out with our efficient mobile laboratory, hooking up to the power, water and steam in each railyard across the line, moving northwest to the cities of Spokane, Pasco, Seattle, down to Portland and San Francisco, and back again to the Twin Cities in Minnesota.

Taylor had carefully negotiated two essential elements for success of the USRR study: that the rail clerks could be examined at their worksite during working hours without their pay being docked, and, at my insistence, that the information we collected on all employees would be held confidential and not provided to railway physicians or the companies. These guarantees clinched the enlistment of the rail brotherhoods. Off we went, then, in 1957, on the first round survey, to compare the



The US Rail car.

risk factors and the medical findings of rail executives, sedentary clerks, switchmen, and right-of-way personnel, among whom Taylor's pilot work had validated different habitual activity and oxygen consumption levels on the job.

The railmen were a jovial bunch and our crew, too, was congenial, working together effectively and examining up to 40 men a day at stations and switchyards across the country. This team developed in this first survey round many of the field strategies that became trademarks of Minnesota population studies over the years: careful planning and pre-negotiations, field testing and pilot studies, clear population definition, census, and recruitment, thoughtful scheduling, on-site quality control, and central data editing, processing and analysis. Taylor was no trained epidemiologist, and may only late have heard the word 'epidemiology'. Rather, he was a physiologist with a penchant for clear thinking and careful methods, along with a lifelong curiosity about the physical activity of humans. He soon became one of the more competent of chronic disease epidemiologists, and an acknowledged expert in recruitment and field operations.

My earliest experience with Henry Taylor in 1954, having chosen to spend a six month's research rotation in the LPH as part of an Internal Medicine fellowship, taught me much about his forthrightness and integrity. On my first visit to the Laboratory, driving a battered green '41 Chevrolet coupe', dressed in a battered

Bavarian hat, and old Navy overcoat, I was accosted by HLT in the Stadium parking lot, as if I were a University student attempting to park illegally. He challenged me brusquely, 'What's your business in the Stadium, young fellow?' We were both relieved when I was able to raise the name of electrocardiographer, Ernst Simonson, as the contact I sought. Not long afterward, engaged in physiological tests in the main laboratory of Stadium Gate 27, he questioned a heart rate I had recorded of 148 beats per minute, saying, 'How did you count 148 beats per minute --counting for a whole minute?' 'I counted 37 beats in 15 seconds', I replied. He was quite aware that no one could keep adequate count of a rapid pulse for a full minute and simply wanted to be sure I wasn't 'guessing'. Our mutual ethical 'blue noses' led much later to the only explosion between us in almost 30 years'association. But that's another story.

The rail survey team was highly competent and compatible and in our working and traveling together we elaborated, by plan and by trial and error, much of the general field experience that the LPH utilized in subsequent operations: that six days running was the limit of effective staff performance, requiring a break; that three weeks running was about the limit of effective staff participation without a brief home leave, and that it was not possible to employ our converted 1895 presidential Rock Island Line sleeping car as a dormitory and still maintain efficiency, etc. The latter led to staff being quartered in quiet motels, and to having pleasant team dinners in attractive restaurants in the evenings to relieve the heavy work routine. We learned care to avoid over-booking participant appointments, particularly the first day of a new location, and other ways to encourage 'happy campers' among staff and participants.

It was a fine field operation, from which we were able to apply what we learned, as well as the USRR forms and procedures and classifications of disease, to the broad overseas operation of the Seven Countries Study beginning in the fall of 1958 in Dalmatia.

There were many adventures 'on the rails', both intellectual and social. We usually had a six-pack of beer in the fridge, and as we traversed the land, held long conversations about the colorful railmen we met, and about the burgeoning new field of CVD epidemiology in which we were involved. On the second round of exams, starting in 1962, I had my soprano saxophone along and often serenaded the countryside from the rear of the Lab car, which usually served as the caboose for the train to which we were attached. We acquired many friends along the line as Taylor and I made contacts to hire and train short-term medical examiners. Numerous American colleagues participated over the course of six years of examinations in two rounds, '57-58 and '62-63, and we were joined by a series of overseas visitors come for training at the new 'epidemiological Mecca' in Stadium Gate 27.

The staffing was exceptional as we began the first round USRR survey, with

Henry Blackburn, Nedra Foster and two subjects in US Railroad mobile lab, 1957.

such experts as Paco Grande assisting at the initial dietary interviews and Jaschka Brozek doing the anthropometric measurements. I, along with Walt Carlson and John Vilandre, and later Pentti Rautaharju, carried out the exercise electrocardiographic monitoring; Nedra Foster and Gail Dolliff handled the blood, urine, and X-ray technical duties, while I shared the clinical exams with our drop-in colleagues. In all it was a happy, yet disciplined and effective operation.

Methods

U.S. railroad employees were chosen because they are largely stable in their specific occupations and in their lifetime employment, and had measured differences in physical activity at work. Moreover, all rail employees are covered by a pension plan for which the Railroad Retirement Board maintains detailed records of employment, disability, retirement, and death. Permission of the companies, of the Retirement Board, and the various labor unions involved, was required, including each local Railroad Brotherhood official. Geographic dispersion of the industry made it impossible to concentrate on a few large centers, so that men had to be examined along the rail lines. All 20 rail companies operating in the northwestern quadrant of the United States, circumscribed by Chicago, St. Louis, San Francisco, and the Canadian border, were involved. Only two companies refused full participation. Companies were asked to supply the names of all male clerks, switchmen,

dispatchers, and executives, aged 40 or more, employed in 1957. Selection from this roster excluded stations with less than 10 employees in these categories, and clump sampling was used. Selection of 30 units ensured proportional representation in each geographical area and each size of urban area.

First contact was made with the general chairman of each union who was asked to write a letter of endorsement. This was reproduced and enclosed in an individual invitation letter to each subject. Lodge meetings were visited by members of the staff beforehand, usually Dr. Taylor or me, and the meeting was advertised throughout offices of the railroad. Union membership lists were checked against the worker lists provided by the rail company. Personal invitations to the survey were then issued and examination dates assigned. The Lab car visited each location at least twice during each of two survey rounds, five years apart. Chief clerks and yard masters and switch tenders were excluded because of unusual pay, or activities different from the general membership of that occupation. Clerks were examined on company time. Clerical desk workers, switchmen, and maintenance of way personnel were representative of sedentary, moderately active, and active groups, respectively. Clerks were sub-categorized as non-sedentary if they had walking and baggage-handling activities. Executives were mixed in their activity level and dispatchers were completely sedentary on the job. Oxygen requirements for each of the several main tasks required of men in the switchmen and clerk occupations were studied in small samples, and data linked with time and task measurements and a dietary survey. The switchmen averaged 600 kilocalories a day more energy expenditure than clerks.

Data were obtained on a population of 8,053 clerks, switchmen and executives employed by the 20 railroad companies in the northwest quadrant of the United States. A sample of 1,163 sedentary clerks, 1,414 switchmen and 363 executives was selected for examination and 74% of the sedentary clerks, 59% of the switchmen, and 68% of the executives responded and were examined.

Cross-sectional Comparisons

The sedentary clerks had been in the railroad industry longer on average than the switchmen but changed jobs more often. There was a homogeneous distribution of parental nationality. Clerks and switchmen were on the same economic level, and switchmen were heavier cigarette smokers. There was no important difference in electrocardiographic items between occupations except for post-exercise ST depression, which was significantly higher in clerks and switchmen. The prevalence of hypertension was not remarkably different, though the executives had fewer men with elevated diastolic pressure.

Prevalence of hypertension increased with relative body weight and with serum

cholesterol concentration. Overweight was greater among the switchmen, least among clerks, and increased in all with increasing blood pressure. The west coast had the highest reported death rate at the RR Retirement Board, Rocky Mountain areas the lowest, and the plain states intermediate. The geographic distribution of measured variables was different for the switchmen, in which case the Rocky Mountain switchmen were thinner and lighter, had lower blood pressure, and smoked less.

Blood cholesterol concentration was not different between occupations or geographical areas. The most striking differences between switchmen and clerks were in relative body weight and systolic blood pressure. Examination of employment records revealed there was no difference in blood pressure of clerks and switchmen at their entry to railway employment, but the switchmen were heavier, indicating occupational selection.

The observed prevalence of coronary heart disease was influenced by a greater rate of withdrawal of younger switchmen with coronary disease compared to clerks.

Five-year Follow-up

The concept behind joining the USRR Study to the comparative spectrum of the Seven Counties Study was described by Henry Taylor and colleagues as follows: 'The railroad industry presented an attractive setting to study the epidemiology of coronary heart disease in contrasting populations because the stability of employment and the extensive records maintained by the Railroad Retirement Board made it possible to evaluate the relevance of particular samples to the industry as a whole and to analyze the effect on incidence rates of withdrawals from the industry, job transfers, etc. Proof of death was required for payment of death benefit.' Moreover, it provided 'the prevalence and incidence of CHD in the large American cohort for comparison with men in other populations with different diets and activities, with respect to the universality of risk factors and whether they had equal weight in all populations.'

The age-standardized prevalence rates of coronary heart disease did not differ significantly between active and sedentary men. Even if they had, the problem with differential retirement of switchmen with coronary disease, the shift to more sedentary occupations, and the larger proportion of switchmen and clerks with heart disease that reported for examinations, would have made interpretation difficult.

After five years, 62 men died from CHD deaths and 124 from all causes. All-cause death rates were higher for active switchmen than for sedentary men, but the difference was not significant. The coronary death rate was lower among switchmen and again, the difference was not significant. Nevertheless, with all occupations pooled, there was a strong and significant relationship between blood pres-

sure and all-causes death, largely confined to the upper 4th and 5th quintiles of blood pressure level. The relationship to skinfold measurement of obesity was not significant. The death rates from coronary disease and all causes increased progressively from never-smokers, to stopped smokers, up to more than 20 cigarettes a day, being 400% higher in the latter than the first category, and three times higher for non-coronary death causes.

Despite the apparent tendency toward concentration of coronary deaths, angina pectoris, and CHD incidence in sedentary classes the 5-year CHD incidence differences were not significant. Smoking was an important factor in each of the occupations, with the rate among non-smokers half that expected, whereas the CHD death rate ratio was 3.6 for heavy smokers after holding blood pressure and cholesterol constant.

Blood pressure, obesity and cholesterol were related to hard CHD criteria and all criteria for coronary death. However, these are univariate relationships, and the relationship with body weight drops out entirely when systolic blood pressure is held constant.

Many more results are to be found in the 10-year and later follow-up data of deaths among the USRR cohort. These have contributed to new insights on cultural differences in the force of risk factors. Follow-up for 25 to 30 years provides understanding of the sometimes different predictive power of physical risk characteristics over the long-term versus the short. The Italian group with Menotti have analyzed these relations in detail, including the late predictive importance of changes in individual risk factors early in the follow-up of Seven Countries cohorts. Ancel Keys reports evidence that body mass and fatness are unrelated with survival to old age, while cigarette smoking consistently predicts early demise.

Conclusion

We learned many things from the USRR Study in its first years, particularly the difficulty to make valid occupational comparisons of CVD rates; much depends on selection at the time of entry into the occupation, and subsequently, when there is selection against active occupations by concentration of coronary events among the less active jobs. We also learned 'the hard way' that the cohort numbers were inadequate for a powerful comparison of active and inactive populations. Some 10,000 to 15,000 men would have been required in each activity class, based on the 5-year CHD incidence we observed in the sedentary group, to demonstrate differences. Details are given in the chapter on Main Results, but the USRR Study was among the first major longitudinal CVD studies in which an independent relationship was *not* found between relative weight or skinfold obesity and CHD rates. On the other hand, the USRR Study confirmed the universality of the main CHD risk factors,

contributing to the strong inference of their causal role, and its data were entered into the American Heart Association Pooling Project, the first formal statistical summary in CVD epidemiology.

In parallel with the cohort studies we studied occupational differences in death rates using death certificates for the entire railway population, industry-wide. The relative risk for sedentary versus active occupations was 1.18 for infarction or coronary death, 1.2 for coronary death, and 1.18 overall for men free of CHD on entry examination. Bias in death rates calculated among men who did not retire or change jobs was avoided by including deaths of all men in the cohort after any job change. Withdrawals from jobs for coronary disease were identical between the two occupations. The Railroad Retirement Board may award disability retirement more readily for men working in switchyards where a heart attack might result in a costly accident. This would explain why coronary deaths, plus disability retirement, accounted for one third of coronary cases among switchmen, but only one sixth among clerks.

The relative risk ratio of 1.18 is, nevertheless, the best estimate available of the true difference in CHD incidence between sedentary and active rail occupations having an average difference in daily physical activity of 600 kilocalories. This compares to risk ratios of 2.2 for blood cholesterol level, 2.1 for systolic blood pressure, 0.95 for relative weight, 1.2 for skinfold thickness, and 1.3 for height. The USRR Study led us to conclude, therefore, that within high-risk cultures, skinfolds, height, relative weight, and job-related physical activity are risk factors of 'a second order of magnitude' for individuals.

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5

THE EAST-WEST STUDIES OF FINLAND

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The Finnish participation in the Seven Countries Study had its origin in an encounter of Martti J. Karvonen (MJK) with Ancel Keys in Minneapolis, May 1954. Finland, with its exceptionally high mortality from cardiovascular diseases (CVD), stood in steep contrast with the Mediterranean nations; moreover, in eastern Finland both mortality and disability due to CVD were markedly higher than in the southwest of the country. MJK, then director of the Physiological Department of the Institute of Occupational Health (IOH) in Helsinki, was further intrigued by the high premature mortality among a population which earned its living largely from heavy forest and farm work, who might have been expected to enjoy the benefits of a physically active, healthy outdoor life. The two physiologists, Keys and Karvonen, agreed that an international study was needed; a protocol had to be worked out and resources obtained for the collaborative effort.

Two years later, in early autumn 1956 a pilot study was organized in two contrasting regions of Finland among the rural population: in the communes of Juuka and Ilomantsi in the east, and Mietoinen, Nousiainen, Vehmaa, Karinainen, Mellilä, and Pöytyä in the southwest. Men and women 20 - 59 years of age who were judged healthy were invited to a survey, which included medical examination, smoking history, anthropometric data, both serum total cholesterol, and its alpha (HDL) and beta (LDL) fractions; and conventional 12 lead ECG's and spatial vector electrocardiograms using Frank's orthogonal system. After the rural fieldwork, the Helsinki Fire Brigade and male executives visiting for annual health checks were also given the same clinical and laboratory examinations. The total number of persons examined was 967, most of them men. Diet and the risk of CHD were to be a major theme.

The 'clinical' team in 1956 consisted of Ancel Keys, Flaminio Fidanza from Italy for analysis of lipoproteins, and from the host country, MJK, medical student Pentti Rautaharju for the ECG, and two women staffmembers for the laboratory and ECG recording. Professor Paavo Roine of Helsinki University was the leader of modern nutrition science in Finland; he joined our team by organizing an independent par-

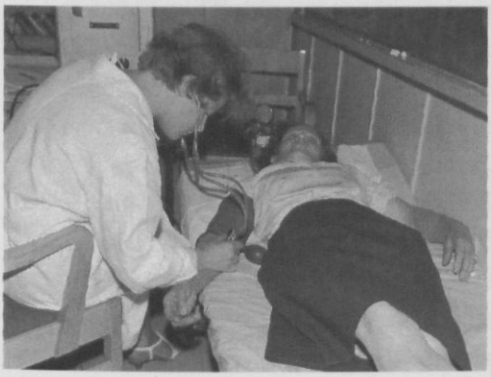
allel East-West project of dietary surveys, closely coordinated with our epidemiological studies and applied to the 1956 survey.

From the 1956 survey we learned how to run a field study. We also grasped that for an unbiased, full picture of the health of a population, total cohorts, instead of ostensibly healthy ones only, must be recruited or randomly sampled. We thus obtained the first valid data on the distribution of variables of interest among these populations. These Finns had higher serum cholesterol than any other major population that had been studied; in the east the values were highest. The Finns thus belonged to the family of nations with high cholesterol and high mortality from coronary heart disease (CHD) and, in fact, appeared to carry the 'world record' in both. Men involved in heavy physical work in the eastern forests had equally high cholesterol level as men in lighter jobs, although they ate more than double the amount of fat. A large seasonal variation was noted in the serum cholesterol level, particularly in the east, with highest values in the winter; timing further surveys to the same season thus appeared a necessary condition for comparable results. The Finnish men also smoked a lot.

Member of the Seven Countries Study

The Seven Countries approach thus began to take shape. Cardiovascular epidemiologists were needed; they had to be trained. In Summer 1957, Esko Orma, MD, with previous experience in experimental atherosclerosis and geriatrics, was sent from the IOH to the University of Minnesota; some months later Sven Punsar, MD, a young clinician from the leading Helsinki unit in cardiology, led by Professor Pentti Halonen, first took part in the Nicotera pilot survey in southern Italy, and then continued on to Minneapolis, where both stayed for a year.

The Finnish Heart Association (FHA) was founded in 1955 at the initiative of a layman, Mr Kullervo Heiskanen, also a staff member of the IOH. Ancel Keys was invited to give a public lecture in Helsinki in November 1955 and then established contact with the FHA and leaders in the health field such as the Director General of Health Services, Professor Niilo Pesonen, the Director of IOH, Dr. Leo Noro, and the Medical Director of the largest Helsinki City Hospital, Professor Pauli Soisalo, an ardent promoter of the FHA. In August 1956 the FHA opened its first health education campaign with a lecture by Paul D. White, the famous U.S. cardiologist; he also visited the team starting its work in Ilomantsi, close to the Soviet border and 'east of Leningrad and north of Anchorage'. The organizational home for the East-West Study was provided by the IOH (until 1974) and then by the FHA (until 1984), when the Finnish National Institute of Health adopted it within the Department of Epidemiology and Health Promotion, directed by Professor Pekka Puska. As the first principal investigator, MJK remained until 1980; he was followed by Sven



Field examination in Finland, 1959.

Punsar until 1984, and since then Professor Aulikki Nissinen, presently Chief of the Department of Public Health and Primary Care, Kuopio University has served. Esko Orma served as full-time epidemiologist from 1962-64, and Sven Punsar followed him, 1964-1984, serving as a largely unpaid volunteer, after his daily hospital work. MJK worked abroad for WHO in the years 1966-67, giving Sven Punsar full responsibility. The project was funded from the U.S. Public Health Service (until 1969) as well as from Finnish sources, among which was first the Yrjö Jahnsson Foundation and later the Academy of Finland; both eventually became long-term supporters. From 1970 to 1989 only Finnish sources were relied upon.

The Epidemiological Surveys 1959 - 1984

Among the eight communes visited in the 1956 pilot Study, one in the east, Ilomantsi, and two in the southwest, Pöytyä and Mellilä, were selected for the main prospective study. Prior to the September 1959 survey the FHA organized a working meeting in August for experts and investigators of the Seven Countries Study, with 11 foreign participants from the United States, Denmark, England, The Netherlands, Norway, Sweden, and Yugoslavia, in addition to the Finnish group.

The IOH in Helsinki and the Laboratory of Physiological Hygiene at Minnesota provided logistic support for the 1959-1969 surveys; premises in Ilomantsi were obtained in 1959 from the Frontier Guard and in the west from the municipal health services. The field work in Ilomantsi was done as a rule during September and in Pöytyä and Mellilä in October, which timing provided similar seasons for the two areas. Several of the August meeting participants from abroad joined the fieldwork for various lengths of time, and got practice in standardization of survey methods, the battery for which now included:

- full medical examination,
- 12-lead resting and post exercise ECGs,

- lung function tests: vital capacity and its subdivisions, maximal breathing capacity, and peak expiratory rate,
- anthropometric measurements,
- blood samples for serum total cholesterol and thiocyanate, a marker for smoking habits,
- questionnaires on personal diet and smoking habits, and respiratory symptoms.

In sub-samples, residual volume and diffusion capacity of the lungs, serum fibrinogen, and blood fibrinolysis were determined. Ian Higgins, of the MRC Pneumoconiosis Research Unit in Cardiff, Wales, took care of standardizing the lung function testing to correspond with that used in their studies. In 1959 1,675 men were examined, about 98% of the total eligible population of men born from 1900-1919. During the first week of the survey an important observation was made: the new standard mercury sphygmomanometers had cuffs with hooks and with too short rubber bags, and thus gave erroneously high blood pressure values, particularly for persons with thick arms. A worldwide pseudodisease, 'cuff hypertension' was thus discovered. It may have improved the sales of antihypertensive medications, but may also have contributed to the apparent epidemiological association of hypertension with body mass and muscularity. Getting specially hand-made, adequately sized cuffs 'cured' the epidemic in Ilomantsi, but many commercial makers of sphygmomanometers were slow in learning this lesson.

Serum total cholesterol levels were now analyzed from refrigerated sera transported by air to Helsinki, and also from duplicate samples dried on filter paper and then sent air mail to Minneapolis. The agreement of the two laboratory series was good; nevertheless the East-West Study preferred to use its own analyses for internal consistency, while for the Seven Countries publications the dried samples, centrally analyzed, were the standard. A parallel dietary survey was carried out on 60 families chosen at random in each field area.

In 1960 the annual follow-up of incidence and deaths was developed among the 1959 examined cohort, the local contact persons recruited, and monitoring started. We had access to all hospital records and information from local physicians. By 1961 the survey data had been transferred to Hollerith cards for analyses in Helsinki, and also had been sent to Minneapolis. The data base was completed by enquiring of the men the age at death of their parents.

In 1962 the oldest men, those born in 1900-1904, were invited to a re-examination; the team consisted of Esko Orma, Henry Blackburn, Pentti Rautaharju, Marja Keinonen, Veikko Kallio, and laboratory staff. A total of 347 men, 92.5% of the survivors, were examined. The battery comprised clinical examination, conventional 12-lead ECG at rest and Frank's orthogonal lead vector ECG on magnetic tape, analyzed with an analog-digital computer. Special attention was devoted to an exact description of angina pectoris, and to the unbiased measurement of blood pressure.

In 1963 Marja Keinonen made a complementary East-West field survey covering a wide age range of men and women; she measured blood pressure blinded and took blood samples for serum total cholesterol. Ilomantsi also attracted a widely travelled otolarygologist, Samuel Rosen of New York, who was making an audiometric survey among adults and children worldwide; defects in hearing proved prevalent in Ilomantsi already from childhood.

In 1964 an International Symposium on Physical Activity and the Heart was organized by the FHA in Helsinki, August 27-29, just prior to the start of the 5-year Seven Countries re-survey. Several of the participants came to see or participate in the work in Ilomantsi, among whom once again was Paul D. White, Henri Denolin from Belgium, Zdenek Fejfar from WHO, Samuel M. Fox, III, Richard D. Remington, Jeremiah Stamler, and Henry Taylor from the U.S.A.. Henry Blackburn and others joined the team for the regular survey work or for special projects.

The 1964, 5-year resurvey aimed at identifying incident cases of CHD, as well as charting the determinants of CHD over a continuum of age. Moreover, the coverage of individual physiological variables and life habits was also widened. Blood samples were taken for total cholesterol, thiocyanate, and coagulation time. All interviews were now taped. The participation rate was again high: 1,529 men in all were examined, 740 in Ilomantsi and 789 in Mellilä and Pöytyä, and the team counted 17 research workers from 9 countries.

ECG Coding and Vector-ECG Projects

One of the early objectives of the East-West Finland component of the Seven Countries study was to develop a standardized system for classification of ECG findings for epidemiological investigations in progress at that time in Finland. This development was initiated in 1954 by Pentti Rautaharju, and was first used in the 1956 East-West Finland survey. Another research objective during this early period was to introduce quantitative methods for analysis of the standard 12-lead ECGs using vectorcardiographic principles. This latter objective was achieved by means of a mechanical vector analyzer invented by Ernst Simonson and constructed by Pentti Rautaharju in 1954.

These early efforts at quantification and standardization resulted in the publication of several reports on normal ECG standards in relation to sex differences, age evolution, occupation and physical fitness level, and hypertensive status. The conventional ECG showed substantial differences in the prevalence of ECG abnormalities among various population samples of ostensibly healthy men, ranging from 13% among lumberjacks in East Finland to 29% among the Helsinki Fire Brigade. Coronary heart disease prevalence was estimated to vary between 4.0% and 8.9%, with the highest prevalence in rural East Finland. Hypertension with ECG evidence

of left ventricular hypertrophy was observed in 8% of the firemen and in 6% of the eastern rural men, but in none of the 99 lumberjacks. The electrocardiogram had clearly proved its validity as a tool in epidemiological studies!

ECG coding efforts in Finland aroused the interest of Ancel Keys, who visited the West Finland survey with Paul White in 1956. In 1958 Dr. Keys arranged for Dr. Rautaharju to join the research group of the Laboratory of Physiological Hygiene, where Henry Blackburn had also been involved for several years in a concentrated effort to develop and validate a standardized ECG classification system for the USRR and other Minnesota epidemiological studies. Dr. Rautaharju and Dr. Sven Punsar, another visiting scientist in Minneapolis from the Finnish team, joined Dr. Blackburn and Dr. Simonson in this intense undertaking, which resulted in the 1960 publication of the Minnesota Code in *Circulation*. This article by Blackburn *et al.* was some time ago reported by the Citation Index as one of the more frequently quoted papers in the entire cardiovascular literature.

The prospects for computer analysis of the ECG emerged during the early 1960s, and electronic tape recording technology was introduced into the East-West Finland Study by Pentti Rautaharju in 1962. The capacity of these early tape recorders and amplifier systems constructed in the Biophysics Laboratory of Otto Schmitt was limited to three simultaneous channels. The recordings were made using the orthogonal ECG leads of the Frank system. The primary focus was on computer analysis of the ischemic ECG response to exercise from tape recordings performed by Pentti Rautaharju and Henry Blackburn in several surveys of the Seven Countries Study. Dr. Hans Friedrich and Dr. Herman Wolf from the Dalhousie group were responsible for the medical engineering aspects of these pioneering projects. In retrospect, the Seven Countries Study was a fertile proving ground in the development of conventional and computerized ECG classification methods. With gradually enhanced power and capacity of electronic ECG acquisition and computer technology, the Dalhousie ECG Program was developed by Rautaharju's team in Halifax. The most recent version of this program (NOVACODE) has emerged as the standard for major national health surveys and clinical trials in the U.S.A.

Studies Outside the Scope of the Seven Countries Basic Program

The East-West project has included the following studies, carried out in addition to the basic Seven Countries program, partly by the core personnel, but largely also by guest investigators from Finland and abroad.

1. Vector electrocardiography project, Rautaharju *et al.*, 1959
2. Random zero blood pressure measurement, Keinonen (Lappi), 1962, 1963
3. Psychological variables, Barry, 1964
4. Pulse wave velocity, Dontas and Herron, 1964

5. Apex cardiography and carotid pulse waves, Heikkilä and Luomanmäki, 1964
6. Heart size by X-rays, Koskela, 1964
7. Lung diffusion capacity, Heinonen, 1964
8. Habitual physical activity, Karvonen, Punsar *et al.*, 1964, 1969
9. ST interval in ECG, Punsar, Pyörälä, and Siltanen, 1968, 1974
10. Heart disease and perceived exertion, Barry, 1969
11. Life changes as predictors of CVD, Rahe and Arajärvi, 1969
12. Thyroid antibodies as risk determinants of CHD, Bastenie *et al.*, 1969, 1974
13. Subjective, medical, and social loss of work capacity, Nygård (Tuomi), 1969
14. Prognostic significance of the ECG, Punsar and Pyörälä, 1969
15. Prognosis of CHD and angina pectoris, Punsar and Karvonen, 1969
16. 'Water factor' project, Punsar, Erämetsä, and Karvonen, 1974, 1979
17. 'Hair study', Punsar, 1974
18. 24-hr sodium and potassium excretion, Karvonen and Punsar, 1974
19. Urinary chromium excretion and atherosclerosis, Punsar, Wolf, and Mertz, 1977
20. Inverse relation of silicon in drinking water and atherosclerosis, Schwarz, Ricci, and Punsar, 1977

A sub-study was made on systolic time intervals in 139 healthy men in western Finland. The data were later used as reference in four published papers related to the use of systolic time intervals in estimating L-R shunt in patent ductus, severity of aortic valve incompetence, power failure in acute myocardial infarction, and prognostic score of acute infarction.

Thyroid function has been among the suspected determinants of atherosclerosis and CHD; thyroid hormone markedly affects the serum cholesterol level. The soil and water in the eastern lake area of Finland are poor in iodine: hypothyroidism as well as compensatory thyroid hypertrophy, goiter, were endemic as long as the diet was essentially composed of local food items which prevailed during the first half of the 20th century. Our men of the East therefore had been exposed in their younger years to iodine deficiency. Thyroid disease is now known also to be associated with autoimmune processes. P.A. Bastenie of Belgium (1971, 1972) observed thyroid antibodies in the blood of CHD patients more often than in others. He proposed to include also the East-West men in his project, and in 1969 blood samples were taken in east and west for:

- thyroglobulin antibodies,
- microsome antibodies,
- protein-bound iodine, and
- butanol extractable versus non-butanol extractable iodine.

In 1974 thyroid function in several of the same men was assessed by determining thyroxine iodine (T_4), tri-iodotyronine (T_3), and thyreotropine (TSH) in serum. Antibodies were more prevalent among those with CHD than among those with-

out; over the period 1969-74 CHD incidence and mortality were also higher among those with antibodies. While the prevalence of antibodies in the east was 5.9% and 6.8% in the west, in the Dalmatian cohort of the Seven Countries Study it was only half that, 3.6%. Thyroid autoimmunity thus emerged as an important risk factor both in east and west, with risk ratios of 1.5-1.9, somewhat lower than smoking, serum cholesterol or blood pressure in the 15-year follow-up.

The East-West Study in 1971 joined the search and identification for a hypothetical 'water factor' as a determinant of geographic differences in the incidence of CVD, as well as of its possible associations with major risk factors of CHD, by analyzing water samples from 339 individual wells serving members of the East-West cohorts. The data were then related to the 10-year record of health and to the 1969 blood pressure, serum cholesterol, and extrasystoles in the ECG; for smoking habits the 1959 data were used. Twenty-two characteristics of water were determined, among them the concentrations of 13 trace elements. In both populations the individual risk of CHD death and incident CHD were associated with low concentration of water constituents. When comparing the two cohorts, CHD was associated with low chromium and with high copper in drinking water. The east-west difference in chromium was confirmed also in the 24-hour excretion rates in urine. At present, these observations add support to the role of antioxidants in atherogenesis.

In further studies the essential elements: selenium, silicon, and iodine were also examined. Silicon concentration in well waters was low in both areas, particularly in the east. Samples of head hair were also collected from the men of the two cohorts and shipped to the laboratory of our co-worker, Professor Klaus Schwarz of the University of California at Los Angeles. He unfortunately died, and the new directors of the laboratory threw away the hair samples (without making contact with us). This example of insecurity in research data (and blindness to the rights of faraway partners of the late eminent scientist) shocked us, making the pursuit of further studies on trace elements unattractive!

Simultaneously, the exterior characteristics of head hair had attracted interest, together with their possible associations with other body characteristics or diseases. Three characteristics of hair were examined: the degrees of baldness and grayness, and the size of hairs. Men who had an advanced degree of baldness had a slightly higher blood pressure and serum cholesterol concentration than other men of similar age. Baldness, however, was unrelated to increased deaths from all causes, CHD, or cancer. Hair grayness was positively related to blood hemoglobin concentration and to absolute and relative body weight. Hair size was greater in western Finns than eastern. The median hair size in individuals was positively associated with body height and blood hemoglobin concentration, and inversely with cigarette smoking.

Dietary salt intake had been proposed as a determinant of blood pressure in the 1960s and 1970s. Previous reports in Finland had suggested a 'moderate' daily intake, 8.3 grams sodium chloride per day. In the 1974 survey 24-hour urine was collected in a representative sample of the East-West men for sodium and potassium analyses. The sodium excretion turned out to be much higher than anticipated, 16.0 g NaCl/24 h in both areas. The intake of sodium thus exceeded the known values for other populations examined up to that time, except for the highest ones reported for regional populations in Japan. At the individual level, however, the correlations between sodium intake and blood pressure were low, as might be expected from a one-day sample of any component of diet in a homogeneous population.

The ECG is a demonstrated useful tool of research in epidemiologic studies of CHD. ST segment depressions in resting and post exercise ECG are common signs of CHD. A new classification of ST segment depressions, modified from that of the Minnesota Code and largely based on experience obtained in the East-West Study, was presented in 1968. In the classification the ST segment depressions were divided in three categories: horizontal or downward sloping ('ischemic') (I), slowly ascending (S), and rapidly ascending (R) ST segment. In follow-up of the men, the categories were found to have different prognostic significances, the R-type post-exercise ST depression being a benign phenomenon.

The Epidemiological Surveys in 1984 and 1989

The planning of the 25-year follow-up survey of the Seven Countries cohorts started in 1982. The aim was to study the trends in serum cholesterol, blood pressure, smoking, body mass index, and pulmonary function in the cohorts between 1959 and 1984. The idea was to provide some insight into the reasons why a rapid decrease in coronary heart disease mortality had taken place in Finland during the 1970s and 1980s. Another aim was to assess the functional, mental, and social capacities of the men growing older and to examine lifestyle-related factors predicting independence at older ages. Altogether, 321 men from the East (94%) and 395 men from the West (93%) participated in the survey, which was carried out in September - November, first in Ilomantsi and thereafter in Pöytyä-Mellilä. The protocol adopted in the previous surveys was strictly followed. In addition, the functional, mental and social capacities, blood sugar level, and drug use were measured. The study team now included experts from different disciplines. Martti Karvonen and Sven Punsar represented continuity in the study.

The analyses of the data started immediately after the survey, and Juha Pekkanen, MD, did his PhD thesis on coronary heart disease during a 25-year follow-up and Ulla-Kaija Lammi, MD, on functional and mental capacity, and predictive factors. The analyses also focused also on assessment of diabetes mellitus and

impaired glucose intolerance as well as vitamin A.

Soon after the 25-year follow-up survey the planning for the 30-year follow-up started. The main aim was to analyze the change of coronary heart disease, diabetes mellitus, pulmonary function, and personal autonomy or independence at old age. Examining the lifestyle-related factors predicting general well-being at old age was also a purpose. The survey was carried out again in September - November 1989 in both cohort areas. Altogether, 470 men were studied (91%), and the survey was more comprehensive than previously. In addition to mental and functional capacities and use of drugs, other parameters related to health status were measured, such as quality of life during the last year of life and reliability and validity of measurement of functional and mental capacities. The 30-year follow-up study was planned jointly with the research group responsible for Dutch and Italian cohorts of the Seven Countries Study.

The results showed that in 30-year follow-up the difference in lifestyle related to coronary heart disease risk factors between East- and West-Finland have largely disappeared or even partially reversed. The predictive value of the baseline coronary risk factors showed large differences during 30 years of follow-up. For instance, smoking and serum cholesterol were strong predictors of risk for coronary heart disease death occurring early and late during the 30-year follow-up period. After 20 years of the follow-up, systolic blood pressure was no longer associated with coronary heart disease risk. In contrast, the highest tertile of Body Mass Index (over 24.7 kg/m^2) was associated with increased coronary heart disease risk only during the later part of the follow-up period.

Glucose tolerance was examined during 25- and 30-year follow-up surveys to test the hypothesis that the genetic susceptibility to non-insulin-dependent diabetes mellitus is the same as that to insulin dependent disease. Also the association between glucose intolerance and specific HLA haplotypes was investigated. HLA haplotype data from a population-based Finnish Study of childhood diabetes were used for predicting non-insulin dependent diabetes and impaired glucose tolerance. Results showed that diabetes-associated HLA haplotypes were present in 94% (85/90) of diabetes subjects, 79% (27/34) of subjects with impaired glucose tolerance and only 13% (3/23) of non-diabetic subjects. These findings support the hypothesis that specific HLA haplotypes exhibit a common genetic determinant for insulin dependent and non-insulin dependent diabetes. Furthermore, HLA is a major genetic determinant of glucose intolerance in elderly Finnish men.

Dietary Surveys 1956-1989

Several dietary surveys have been carried out in Finland since 1956 in connection with the epidemiological studies on cardiovascular diseases. The dietary surveys

were planned and put into practice through the Department of Nutrition Chemistry, later the Department of Nutrition, University of Helsinki, by Professor Paavo Roine, Head of the Department, as principal investigator between 1956 and 1969, assisted by Dr. Maija Pekkarinen, who was responsible for the field surveys. Statistical help in the selection of the men and participating families, and in data analysis, was received from the Institute of Occupational Health (M. Pol. Sc. Jaakko Kihlberg) and later from the Computing Center, University of Helsinki. Dietary surveys were carried out in East and West Finland altogether six times in 1956, 1957, 1959, 1964, 1969, and 1989. The 1989 survey was carried out by Dr. Leena Räsänen and Dr. Marja Mutanen. The methods used were either precise weighing or dietary history interview. University students majoring in nutrition collected food consumption data and calculations on energy and nutrient intakes were based mainly on Finnish food composition tables.

Dietary surveys in 1956 and 1957 were carried out in the same areas in East and West Finland as the medical studies. In 1956, 42 families from each area were studied with the weighing method in June, when the diet was monotonous because of the scarcity of fresh vegetables and fruits. For seasonal variation, 40 families were studied again in January 1957. During seven consecutive days all items used in food preparation, during and between meals, as well as table waste, were weighed, with the assumption that the qualitative character of the diet of the family was also a satisfactory indicator for that of the men.

Bread, milk, butter, and fish consumption was higher in the East, and that of vegetables, margarine, and eggs was higher in the West. The total intake of energy and nutrients was similar between seasons and areas. Dietary fat was more saturated in the East than in the West, and the intake of iodine, ascorbic acid, and vitamin E was higher in the West.

The diet and serum cholesterol levels of 110 forestry workers were studied in 1959, separately from the Seven Countries Study cohort, in 15- to 66-year-old lumberjacks, who had their meals in barracks, and the total amount of food consumed in each camp was estimated from the book-keeping records of the cooperative. The large consumption of cereal products, butter, and meat products was noteworthy, with a mean daily energy intake of 4,763 kcal, almost half of which (45%) was derived from fat. The average total fat intake was 237 grams per day, of which milk and butter covered 60% and meat 30% of the total. Though the dietary fat was thus highly saturated, the serum cholesterol levels of the lumberjacks (246-274 mg/100 ml) were similar to those of other men in the local population.

The dietary survey in the fall of 1959 explored the possible role of dietary fat in the etiology of cardiovascular diseases using population (ecologic) correlations in all the Seven Countries cohorts. Altogether 30 families from West and 30 from East Finland participated in this survey, randomly selected from those families of men

who participated in the cardiovascular disease study at the same time. The food consumption of the men, in addition to that of the families, was studied separately, by precise weighing for one week. The diet was typically Finnish, the main energy sources being cereals, milk and milk products, sugar, meat and potatoes, and average energy intake was 3,760 and 3,805 kcal for men in the West and in the East, respectively, of which fat contributed 35.4% and 39.2% of the total energy intake. In the eastern area the fats used were significantly more saturated than those used in the western part of the country. With the exception of vitamin A, other nutrients did not present any regional differences.

In addition to the precise weighing study conducted among 60 families, dietary interviews were carried out among the 1,676 men participating in the Seven Countries cohort in 1959 (817 men in the East and 859 men in the West), to obtain a general view about the food habits of a larger group of men than was possible in the restricted weighing surveys. In the interview the consumption of only main foods was asked. Then, 30 years ago, the families had two main meals and three to five snacks a day; energy intake from the meals was higher in the afternoon. The energy value of food lost in food waste was about 11% of total energy. The differences between weekdays were rather small, though meals on the weekend differed clearly from those on weekdays.

A 5-year follow-up study was carried out in January 1965 with 48 subjects who had participated in the study in 1959. The consumption of cereals, potatoes, milk, and butter was lower than five years earlier, while consumption of meat and fruits had increased and that of vegetables decreased, both in the East and the West. A small decrease in total fat intake was found in the eastern area, but not in the west, where the contribution of fats to the total energy was actually higher than in 1959. During the preceding five years' period the men had gained weight, but it was not reflected in skinfold thickness. Blood cholesterol levels of men were somewhat higher than earlier in both areas.

A dietary history interview survey was carried out in connection with the second round medical study in the fall, 1964, with 319 men in the East and 764 in the West, focusing on the use of table fats, other foods rich in fats, and carbohydrate-rich foods. There was higher consumption of sugar, butter, and meat in the East than in the West, whereas the use of cereals, potatoes, and eggs was higher in the West. Contribution to the total energy intake by fats was 43% in the East and 40% in the West. The daily intake of dietary cholesterol was high in both areas, 666 mg in the West and 616 mg in the East. The men in the West were somewhat taller and heavier than in the East, and also their skinfolds were thicker. Blood cholesterol levels of men were higher in the East (290 mg/100 ml) than in the West (266 mg/100 ml).

In the fall of 1969 the diets of 612 men in the East and 694 men in the West were re-examined by applying a more detailed dietary history method than that used in

1964. The consumption of potatoes, sugar, and butter was lower, and that of cereals higher, than in 1964. The men in the East used more fish, vegetables, fruit, and berries than men in the West. The amounts of sugar, butter, and meat in the diet were quite similar in both areas.

During the 1964-69 period the dietary fat intake of the men in the East had decreased from 43 to 39% of total energy. Milk and meat together provided about 90% of the total fat intake in both areas. Fat was still highly saturated, more in the East than in the West. The diet of men in the East contained more carbohydrates than five years earlier but remained almost unchanged in the West. The cholesterol content of the diet showed an increase in both areas. In spite of the lower energy intake the men had gained weight, and skinfolds were thicker than in 1964. Blood cholesterol values in the East, however, were lower than earlier (East 276 mg/100 ml, West 262 mg/100 ml).

In dietary studies, nutrient intake data are usually based on food composition tables. The calculated values of nutrients from the studies of 1959 and 1965 were in part checked by chemical analyses. In 1959 the checking study included the diets of 10 men in the East and 10 in the West; in 1965, 24 men from both areas. Samples corresponding to the mean daily amount of foods consumed by each man during the survey period were collected at their homes. Food samples were analyzed for water, ash, protein, total fat, and fatty acids. In 1959 the fatty acid determinations were carried out in the Laboratory of Physiological Hygiene, University of Minnesota, U.S.A, by Dr. Joseph T. Anderson. Other analyses were performed in the Department of Nutritional Chemistry at the University of Helsinki. The results of these analyses were compared to the calculated nutrient intakes of the men. The comparison showed such great agreement, particularly in the mean values of protein and fats, but also in those of carbohydrates and total energy, that further chemical analyses were not considered necessary. It also showed the reliability of Finnish food composition tables used in the calculations.

All 48 food samples of the 1965 study were used for analyzing the following mineral elements: Fe, Cu, Mn, Na, K, Ca, P, and ash. Analyses were done in the Institute of Food Chemistry and Technology at the University of Helsinki under the leadership of Professor Pekka Koivistoinen. The results showed a linear correlation between the mineral intake and energy intake. Low contents of iron and copper seemed to be typical for the Finnish diet. The question has risen whether the intake of these elements was adequate, especially in subjects having low energy expenditure and intake.

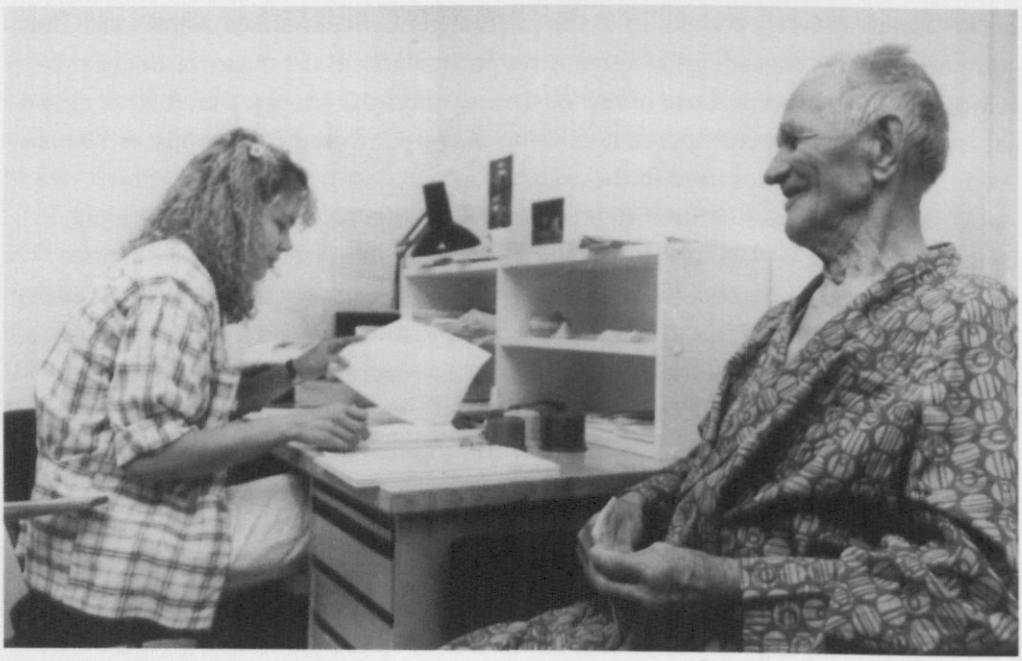
The content of chromium and selenium in the diet of men was based on average food consumption data obtained from the dietary surveys of 1959, 1965 and 1969, using food composition data from chemical analysis of the mineral content of Finnish food. The daily intake of chromium was 41 to 45 µg and that of selenium 21

to 34 μg in the eastern area. The corresponding figures in the western area were 37 to 40 μg for chromium and 19 to 22 μg for selenium.

As a part of the 30-year follow-up survey of the Finnish cohorts, the food consumption and nutrient intake of the men was investigated again in September-October 1989. Of the original participants, 524, 70- to 89-year-old men were still living. A random sample of 298 men was chosen for the dietary interview. Complete dietary history interviews were obtained from 227 (43.3%) men. The dietary history method which had been used in the studies in 1964 and 1969 was modified in 1989 because of the advanced age of the subjects and the great increase in the number of foods available. The period covered by the interview was the previous month instead of the previous year, as before, and interview sheets were much more detailed to include 190 precoded food items. An illustrated booklet with 126 color photographs of various portion sizes of foods was used for estimation of portion sizes. Interviews were conducted in the local health centers (54.4%), at the subject's home (44.3%), or in a hospital (1.3%). The subject's wife or some other person assisted with the interview in one-third of the cases.

Men in eastern Finland consumed considerably more rye products, vegetables, and berries and also sour milk, fish and fish products, than men in western Finland, who consumed more fruits, cheese, eggs, and alcoholic beverages. In both areas the diet in 1989 contained about one-third less potatoes than in the 1960s, while the

Dietary survey in Finland, 1989.



energy-adjusted amounts of vegetables, fruits, and berries had doubled compared to the situation in 1969. Fifty per cent of the butter had been replaced by other dietary fats such as soft margarines. In the western area the amount of fish was three times higher in 1989 than in 1969.

The quality of the diet in the East appeared to be somewhat 'better' than in the West; for example, the intake of dietary fiber, and several minerals and vitamins, was clearly higher due to the greater consumption of rye, vegetables, and fruits, and also the lower energy intake from fat and alcohol. The nutrient density of the diet overall was higher in this most recent survey than in the earlier ones. The dietary history data collected from the 227 elderly men in 1989 showed that diet in old age can comply with general recommendations, and is quite comparable to that of younger age groups.

A longitudinal analysis has recently been completed on the changes in diet of men who participated in the detailed dietary survey both in 1969 and in 1989.

The General Importance of the Dietary Surveys

The main purpose of the dietary studies was an attempt to identify the dietary factors associated with the high incidence of cardiovascular diseases in Finland. Besides this, these surveys have provided information concerning the characteristics and the development of the Finnish diet in general. The collected data reflect changes which have taken place in the diet of the rural population since 1956. They also show the changed importance of seasonal and regional variation. The development of the dietary survey methodology, which has been an integral part of these studies, has been valuable for other dietary surveys in Finland. Since the 1950s dozens of nutrition students have had an opportunity to participate in the fieldwork. Furthermore, more than 10 of them have written Master's Theses on the results of these studies. In conclusion, this series of dietary studies appears to have been of great value for the development of nutrition research in Finland.

Continuation of the Follow-up after 30 Years

Because of concern about the health status of the elderly, it was of great interest to have a further follow-up of the original Seven Countries cohort. Therefore a postal survey was conducted among men still alive in 1992. Information was collected about lifestyle factors, functional and mental capacity, and self-perceived health. Recently the decision was made that similar information will be collected in a 35-year follow-up survey in 1994.

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6

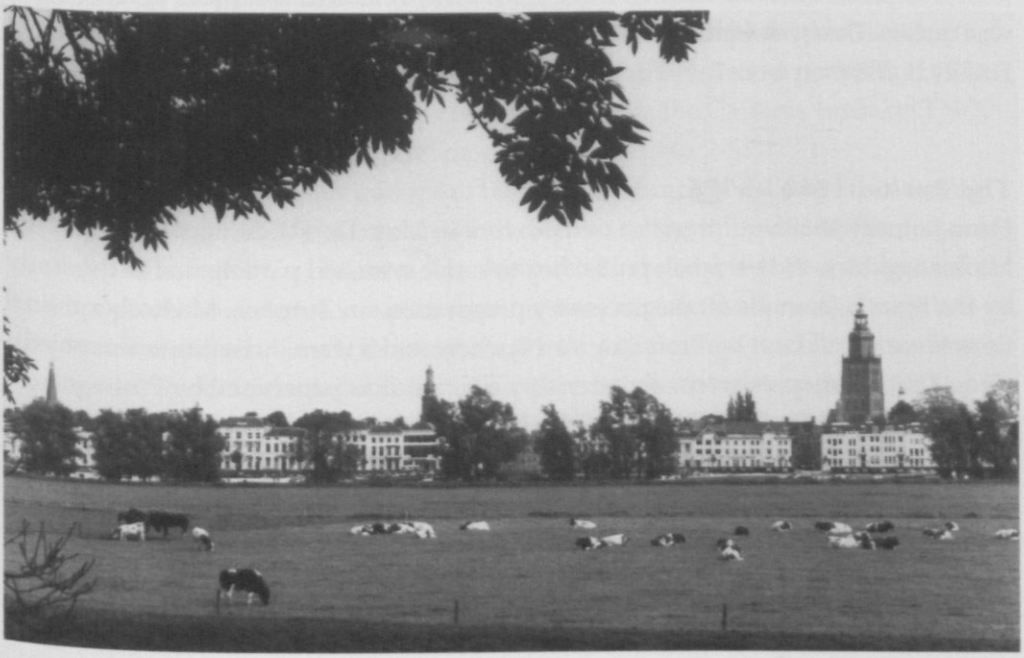
STUDIES IN ZUTPHEN

D. Kromhout

The Netherlands joined the Seven Countries Study due to personal contacts between Professor Ancel Keys and Professor M.J.L. Dols, Chairman of the Netherlands Nutrition Council, which developed during joint work on United Nations committees. Professor Dols contacted Professor Muntendam, Secretary of State for Public Health, about the possibility to join an international study on risk factors for atherosclerotic complications. A fellowship of the Council of Europe enabled Dr. Louise M. Dalderup to join the pilot study in Nicotera, a small village in southern Italy, in October 1957.

Vital to the organization of a similar study in the Netherlands was this contact with Professor Keys and his co-workers during the pilot study, meeting the enthusiastic investigators of different interested countries (e.g. England, Finland, France,

Town of Zutphen.



Greece, Italy, Japan and the United States), observations of equipment and methods, and discussions about pro's and con's of the study. Dr. Dalderup's presence from the unloading of the equipment, its arrangement and the start of the actual fieldwork, gave her an excellent opportunity to study the logistics, see the interactions between members and the composition of the team, and observe the schedule to examine participants.

Thereafter it was decided that the Netherlands should join this international study. A committee on 'Nutrition and Atherosclerosis' was established by the Netherlands Nutrition Council under chairmanship of Professor F.S.P. van Buchem. Other members of the committee were Dr. E.H. Groot, Professor C. den Hartog, Professor G.A. Lindeboom, Professor H. Mulder, Professor P. Muntendam and Professor A. Polman. In 1959 Professor Van Buchem was appointed principal medical investigator and Professor Den Hartog as principal investigator for the dietary studies. Professor Muntendam became chairman of the committee on 'Nutrition and Atherosclerosis'. Additional money was raised to supplement the grants obtained by Professor Keys from the U.S. Public Health Service.

The town of Zutphen, located in the eastern part of the Netherlands, was selected for the Dutch contribution to the Seven Countries Study because there was little mobility of the population, and an earlier investigation for the WHO by Dr. C.A.A. Bramlage, Institute of Social Medicine, University of Leiden (Director: Professor P. Muntendam), had shown the willingness of the citizens to participate in an epidemiological study. In 1960 the number of inhabitants of Zutphen was about 25,000. For this investigation, all men born between 1900-1919 who had lived in Zutphen for at least five years were selected. Of these 2,450 men, a random sample of 4 out of 9 was drawn. Due to financial limitations, only about 1,000 men could be examined. Finally, 1,088 men were invited for the study.

The Period 1960 - 1975

From January 1960 until the start of fieldwork in May, Dr. Dalderup, Dr. E.E.J. Marler and Mrs. W.B. Buchel, public health nurse who had participated in the study by Dr. Bramlage, made all the necessary preparations in Zutphen. Medical examinations were carried out by Professor Van Buchem and a team including seven physicians. Dietary surveys were carried out by six dietitians supervised by Professor Den Hartog and Dr. Th.F.S.M. van Schaik. Of all men invited, 908 were medically examined, 1,049 participated in the dietary survey and 872 men (aged 40 - 59) participated in both the medical and dietary survey. Much help was given by local people, including Dr. J.W. Eerkens, director of one of the local hospitals, E.B. Bosschieter, internist, Mrs. A.H. Thomassen-Gijsbers, nurse, Mrs. J. Brands-Thomassen, Mr. and Mrs. H. Bogers, and many others of the local Red Cross

Frans van Buchem reading ECG's, Zutphen, 1960

ECG taken by Ans Thomassen, Zutphen, 1965

Organization. Without their enthusiastic and practical help the study would not have been realized.

In the period 1960-1973 the core medical examination was repeated annually by Professor Van Buchem and collaborators. E.B. Bosschieter, internist, who was involved in the study from the beginning, became co-investigator in 1966. The dietary surveys were repeated in 1965 and 1970 by Professor Den Hartog and Dr. Van Schaik. During this period several additional investigations were carried out. Between 1960 and 1963 comparative dietary studies were carried out in small subsamples and in 1960 and 1963 an examination of the ocular fundus was done. In 1965 an extensive study on energy expenditure and lung function was carried out by investigators of the Netherlands Institute of Preventive Medicine TNO, Leiden. In 1967 blood groupings and uric acid determinations were carried out. Fasting blood glucose determinations were made in 1968, and a complete glucose tolerance test carried out in 1970 as was Protein Bound Iodine (PBI). Between 1964 and 1971 blood lipid and lipoprotein levels were determined by the Gaubius Institute TNO, Leiden, and the data used in several case-control studies.

In data analyses and publications of the Zutphen Study most emphasis during the first 15 years was on hypertension and electrocardiography due to the personal interests of Professor Van Buchem. He also published a case report of congenital beta-lipoprotein deficiency in a participant in the Zutphen Study with a very low total serum cholesterol level, showing his primary clinical interest. Professor Den Hartog and Dr. van Schaik published descriptive studies of dietary data.

The Period after 1975

Professor Van Buchem resigned as principal investigator of the Zutphen Study in 1974, and Dr. Dalderup looked after the study in 1976 and 1977. In 1977 the committee on 'Nutrition and Atherosclerosis' of the Nutrition Council asked Professor

Kromhout to write a plan for analysis of the data collected in the Zutphen Study. That plan was accepted and Kromhout became the principal investigator of the Zutphen Study in 1978.

Dr. Dalderup started preparations for a new survey round in 1976. In 1977, 500 men were examined and in 1978, 111 men, with a response rate of 91%. Kromhout submitted a grant application for a 20-year follow-up study in 1980, but the grant application was not funded, with the argument that analyses of collected data were more important than new examinations.

In 1978 Kromhout, in collaboration with the medical administration department of the Nieuwe Spittaal Hospital in Zutphen, started a mortality register for participants in the Zutphen Study. The morbidity history of men who died was summarized by Dr. E.B. Bosschieter, based on information present in hospital records. The morbidity histories of all participants in the Zutphen Study covering the period 1960-1985 were coded in a standardized way in 1986 by one physician, Dr. M. Drijver. Information on cause of death according to the International Classification of Diseases of men who died between 1960 and 1985 was obtained from the Central Bureau of Statistics (CBS). The collaboration with Dr. L.M. Friden-Kill of the CBS is recognized with gratitude.

Before 1978 information on the major risk factors was computerized by IWIS-TNO, Rijswijk. However, information on occasionally determined risk factors was not computerized. Thus, all dietary data had to be coded and entered into the computer file,which was carried out by grants from the Nutrition Council. Drs. C. de Lezenne Coulander played a central role in preparing the data sets before statistical analysis could start.

In 1980 Kromhout obtained a fellowship from the Netherlands Organization of Scientific Research (NWO) to work and study for one year at the Laboratory of Physiological Hygiene, School of Public Health, University of Minnesota, Minneapolis, Minnesota (Head: Professor Henry Blackburn). During this year he took a Masters of Public Health degree in Epidemiology. Kromhout prepared in collaboration with Professor Blackburn and Professor Keys a grant application for extensive analyses on diet and chronic diseases in the Seven Countries Study. Finally, he started analyses of the Zutphen dietary data and wrote four papers on the dietary pattern of Zutphen men in the period 1960-1970, dietary determinants of body fatness and serum cholesterol, and the relation between diet and 10-year mortality from coronary heart disease. After his return to the Netherlands in 1981, he started extensive analyses in collaboration with Cor de Lezenne Coulander.

In 1984 a grant application was submitted for a new round of fieldwork to study lifestyle factors and chronic diseases in 1,000 men, aged 65-84, in Zutphen. This grant application was funded in 1985 by the Netherlands Prevention Foundation. Of the 1,088 men selected in 1960, 555 were still alive on January 1, 1985. Of the

remaining 1,075 men, aged 65-84, in Zutphen, a two-thirds random sample was drawn. In total, 1,266 men were invited for the study and 939 (74%) participated. The 721 survivors were invited for a re-examination in 1990 and 560 (78%) persons were examined.

In 1985 and 1990 extensive survey examinations were carried out. Physicians asked for information on the prevalence of major chronic diseases and smoking habits of the participants using a standardized medical questionnaire. A physical examination was carried out, including blood pressure and anthropometric measurements. An electrocardiogram was taken, and blood collected for determination of total and HDL cholesterol, hematologic, hemostatic, and clinical chemical variables. A dietary survey was conducted at home by dietitians using the cross-check dietary history method. Finally, participants filled out a lifestyle questionnaire providing information on demographic variables, occupational history, daily activities, subjective health, life events, loneliness, coping, and future orientation. A glucose tolerance test was carried out in 1990, and blood glucose and serum insulin were measured fasting, and one and two hours after a 75-gram glucose load. In the 1990 survey information was also collected on functional and mental capacities of the participants. In 1993 the information on lifestyle, functional, and mental capacities was collected again in 389 of the remaining 553 (70.3%) men. Also, four tubes of blood were collected for analyses of total and HDL cholesterol, glycosylated hemoglobin, HLA-typing, and storage of leucocytes.

Since 1985 more possibilities have become available for automation of the morbidity and mortality data. Hospital discharge data since 1985 of participants in the Zutphen Study were provided by the 'Nieuwe Spittaal' hospital, and coded cancer data of the cancer registry have been obtained since that time. All this greatly facilitated the complete morbidity and mortality follow-up of the Zutphen men, and made much broader analyses possible. Besides traditional analyses on the relation between lifestyle factors and the incidence of and mortality from chronic diseases, other aspects of health can be analyzed in relation to characteristics of the men. The

Edward Bosschieter taking bloodpressure, Zutphen, 1985

physical, mental, and social aspects of health have thereby been integrated, physical health measured by physical examination, medical history, physical performance and functional capacities, mental health by different questionnaires, (e.g. Mini-mental State Examination and Zung depression scale) and social health by questionnaires about social contacts, marital status, and loneliness.

Results since 1980

In analyses of Zutphen data collected up to 1985, emphasis was placed on dietary data. They have been analyzed descriptively, and in relation to biological risk factors and incidence and mortality from chronic diseases. The results of these analyses are summarized here.

Changes in dietary and nutrient patterns during 10 and 25 years follow-up have been described in two papers (Kromhout 1983a, Kromhout *et al.*, 1990). These analyses showed that energy intake in this aging cohort decreased by 800 kcal/day between 1960 and 1985 due to a decrease in the consumption of bread, potatoes, legumes, vegetables, eggs, milk, edible fats, and sugar. On the other hand, an increase was observed in consumption of fruits, alcoholic beverages, nuts, and pastries. Results of studies on validity of retrospectively assessed dietary intake data, and on reproducibility of dietary intake data, have also been reported (Bloemberg *et al.*, 1989a,b).

Dietary variables were also analyzed in relation to biological risk factors. Energy intake was inversely related to indicators for body fatness (Kromhout, 1983b). Body weight, an indicator of energy balance, was positively associated with serum cholesterol level (Kromhout, 1983c). Alcohol was positively associated with blood pressure, and calcium and potassium intake was inversely related to blood pressure (Kromhout *et al.*, 1985a). Saturated fat and dietary cholesterol were related to decreased glucose tolerance, in contrast to the positive effect of dietary fiber and sugar (Feskens and Kromhout, 1990).

Several analyses were carried out on the associations between different dietary variables and mortality from chronic diseases. Dietary fiber was inversely related to 10-year mortality from total cancer and, in univariate but not in multivariate analyses, to mortality from coronary heart disease. (Kromhout *et al.*, 1982). Energy intake, a 'proxy variable' for physical activity, was inversely related to 10-year mortality from coronary heart disease (Kromhout and De Lezenne Coulander, 1984). An inverse relation was observed between fish consumption and 20-year mortality from coronary heart disease (Kromhout *et al.*, 1985b). This paper was recently selected as a Citation Classic by Current Contents. Dietary cholesterol was positively associated with 20-year mortality from coronary heart disease (Kromhout *et al.*, 1985b). Vitamin C intake was inversely related to 25-year mortality from lung can-

cer (Kromhout, 1987). Sugar consumption was positively, and calcium intake was inversely, associated with 25-year incidence of gallstones (Moerman *et al.*, 1993).

In recent years interests of the investigators of the Zutphen Study has broadened. The predictive value of classical risk factors was studied, including repeated measures. Physical activity was studied in relation to other coronary heart disease risk factors. Occupational exposure was studied in relation to the incidence of chronic non-specific lung disease. Subjective health was evaluated as a predictor of mortality.

A casual serum cholesterol value was found to be a long-term predictor of coronary heart disease incidence in Zutphen men (Kromhout *et al.*, 1988). It was also shown that the predictive power of a casual serum cholesterol determination decreased with increasing age (De Vries *et al.*, 1993). This was partly due to selective mortality of relatively young men with relatively high serum cholesterol values. Blood pressure was an independent risk factor for coronary heart disease and stroke. The strength of the associations improved much by averaged data from repeat measures (Keli *et al.*, 1992, De Vries *et al.*, 1993).

Subscapular skinfold thickness and cigarette smoking were independent predictors of diabetes incidence (Feskens and Kromhout, 1989). Glucose tolerance was an independent predictor of coronary heart disease incidence (Feskens and Kromhout, 1993). Diabetics, compared with non-diabetics, had increased risk of fatal coronary heart disease and incidence of peripheral arterial disease. (Feskens and Kromhout, 1993).

Physical activity of retired men was measured with a questionnaire on daily activities developed by Professor Morris, London School of Hygiene and Tropical Medicine. This questionnaire has been validated against the doubly-labelled water method (Saris *et al.*, 1993). Descriptive data from the 1985 survey showed that the elderly Zutphen men were active compared with their American counterparts (Caspersen *et al.*, 1991). A significant inverse relation was observed between physical activity and HDL cholesterol. When individual activities were related to other coronary heart disease risk factors, an independent association was observed between gardening and HDL cholesterol level.

Prevalence and incidence of chronic non-specific lung disease (CNSLD) was higher among workers in agriculture, and in the paper and construction industries, compared with white collar workers (Heederik *et al.*, 1989). The incidence of CNSLD was also positively associated with intake of linoleic acid. However, the consumption of apples and alcohol was inversely related to CNSLD incidence (Miedema *et al.*, 1993).

Total mortality was twice as high among small business owners and blue collar workers than in professionals (Duykers *et al.*, 1989). Subjective health was also an independent predictor of total mortality. Men who rated themselves as not feeling

healthy in 1985 had a 5.4 times higher mortality from all causes during 5-years of follow-up compared with men who felt healthy (Pijls *et al.*, 1993). This association was independent of the prevalence of chronic diseases and levels of major risk factors at baseline.

Acknowledgments

The Zutphen Study was initiated by Professor F.S.P. van Buchem in 1960. E.B. Bosschieter M.D. became co-investigator in 1966. Professor van Buchem withdrew as principal investigator in 1974. Dr. Louise M. Dalderup guided the Study in 1976 and 1977. Professor Daan Kromhout became principal investigator of the Zutphen Study in 1978.

The 1985 survey was organized by Daan Kromhout in close collaboration with Gatske L. Obermann-de Boer M.D. and Mathilde van Kampen-Donker Ph.D. The medical team was led by Professor A.C. Arntzenius, cardiologist, physicians E.B. Bosschieter M.D., A.H.A.M. Bolsius M.D., A.B, van Haaften M.D. and A.F. in 't Veld M.D. Ans H. Thomassen-Gijsbers played a central role in the local organization and was responsible for the survey of non-respondents. Marianne R.T. van Haaren-Bouterse M.Sc. coordinated the dietary survey that was carried out with the help of 25 dietitians. Cor de Lezenne Coulander M.Sc. and Bennie P.M. Bloemberg PhD. coordinated quality control of the collected data and organized the data sets. Essentially the same persons carried out the 1990 survey, with a few changes. Bennie P.M. Bloemberg Ph.D. replaced Mrs. Van Kampen-Donker in the coordinating team and the dietary survey was coordinated by the dietitians Ester Goddijn and Annemarie Jansen. Edith J.M. Feskens Ph.D. coordinated the biochemical determinations, including the glucose tolerance test and also coordinated fieldwork activities in 1993.

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7

STUDIES IN RURAL ITALY

F. Fidanza and A. Menotti

Beginning in 1952 cross-sectional surveys of different populations were carried out in Naples and elsewhere by Flaminio Fidanza in collaboration with Ancel Keys. They showed that serum cholesterol was related to fat intake (and particularly saturated fatty acids) and that areas with low cholesterol values were characterized by low prevalence of coronary heart disease (CHD). It was difficult to identify appropriate population samples having internally contrasting subgroups because confounding variables could be introduced in comparisons made between socio-economic classes. Therefore it was deemed necessary to set up, in parallel, longitudinal studies on men in areas differing in diet or in the alleged incidence of CHD, or both. Finally, rural areas characterized by simple agricultural pursuits were selected for drawing 'chunk' samples of men aged 40-59.

A pilot survey, led by Alfonso Del Vecchio and Flaminio Fidanza, was carried out in September-October 1957 in Nicotera, Calabria, near the toe of Italy. That rural village was selected because Del Vecchio, first medical student and then intern at the Institute of Human Physiology of the University of Naples, was a native and provided introduction to the community. Vittorio Puddu, then Director of the Center for Cardiovascular Diseases of the St. Camillo Hospital in Rome, was responsible for all clinical aspects. Headquarters of the survey was in a rented house in the center of Nicotera. The field staff included Domenico Cotrone, cardiologist of Rome, Louise Dalderup, internist of Amsterdam, Mario Mancini, internist of Naples, and others for anthropometric measurements and ECG recording. Major international participants in this pilot survey were Ancel and Margaret Keys from Minneapolis, Ratko Buzina from Zagreb, Martti Karvonen from Helsinki, Noboru Kimura from Fukuoka and Paul Dudley White from Boston.

The survey was no easy matter. Because a Swedish Elema ECG machine was used, and it was very difficult to obtain the proper paper, some of us spent part of the afternoons and sometimes evenings cutting down larger-sized paper which was more available. Moreover, there were no hotels in Nicotera, the closest being the Hotel Jolly in Gioia Tauro, about 30 km south. The cobblestone road was terrible, and by car we were jolted for an hour each way. On the other hand, the 'invasion' of

an American TV team for a documentary of the study was very rewarding for us and for the local people. Paul White was captured on film auscultating patients with his famous gold stethoscope.

In August 1958 Flaminio Fidanza carried out, in cooperation with the Center for Cardiovascular Diseases of Ancona, a pilot epidemiological survey on a group of people in Montegiorgio, in Marche, achieving a very high response rate. In the same year, the formal research program and Seven Countries surveys, launched by Ancel Keys and his staff, became operative. Accordingly, in 1959 we created in Italy a Supervisory Committee made up of Flaminio Fidanza from Naples, Arrigo Poppi from Bologna, and Vittorio Puddu from Rome. We met in January 1959 to select three rural areas in Italy contrasting in diet and geography, and to prepare a financial plan of the study to be conducted during the next six years. For an example of southern Italy, it was decided to re-examine the subjects of Nicotera using the new standard methodology adopted by the international Seven Countries Study. For central Italy, the village of Montegiorgio was selected because Flaminio Fidanza grew up in that area and because of the success of the pilot study there in 1958. For northern Italy, Arrigo Poppi proposed the village of Crevalcore because Augusto Pezzoli, the Director of the local hospital, was a good friend. Due to shortage of funds, and similarity with the preliminary results obtained in Crete, the survey planned for Nicotera was canceled.

After approval of USPHS Grant H-4672, the first Italian field survey started in February 1960 in the village of Crevalcore, located about 30 km north of Bologna in the flat and fertile Po Valley. Examinations were conducted in the local Barberini Hospital. Mr Loris Manfredi, mayor of Crevalcore and authoritative member of the local Italian Communist Party, was very cooperative. The municipal guard, Ivo Donini, and his younger colleague, Alfonso Barbieri, were of great help in finding and inviting the 1019 men aged 40-59, resident of the village proper for at least five years. Subjects resident in peripheral hamlets were excluded. Thanks to their help, and that of Gino Cavicchi, a physician in the local hospital, we achieved an excellent response rate (98.5%). The basic field staff included Flaminio Fidanza from Naples, general coordinator; Marisa Todesco, cardiologist from Bologna; Bruno Imbimbo, internist from Naples; Giancarlo Ghironzi and Giorgio Baldacci, both internists from the Republic of St. Marino, Angelo Pezzella, cardiologist from Rome, Ivan Mohacek, internist and cardiologist from Zagreb, and other people dedicated to the anthropometric measurements and the ECG recording. Major international participants and consultants were Ancel Keys, Henry Blackburn, and Ernst Klepetar from Minnesota. In Crevalcore, we experienced good but rich meals. The lack of a reasonable hotel compelled us to travel every day back and forth to Bologna by train or car.

In April of the same year we moved to Montegiorgio, a hill village located in the Marche, about 30 km inland from the Adriatic Sea. Headquarters there was set up

in the new town hall. There we received excellent cooperation from the mayor of Montegiorgio, Mr. Ortelio Ortenzi, and the municipal guard, Guerrino Alessandrini, was of great help finding and inviting the 726 subjects aged 40-59 who participated enthusiastically, achieving a top participation rate of 99.2%. The field staff was the same as in Crevalcore while added international consultants were Edvin Ferber and Branka Tiefenbach, both from Zagreb, Paavo Roine and Maija Pekkarinen, both from Helsinki, Christ Aravanis and Demetrios Lekos from Athens and again, Paul Dudley White from Boston. Picnics and home meals with the local farmers were particularly rewarding. While our hotel was 20 km away in Fermo, the road was good, and we enjoyed excellent fish dinners in Porto S. Giorgio on the Adriatic coast.

Dietary surveys of subjects in all three Italian areas were carried out by a staff of four nurses of the Italian Ministry of Health, coordinated by Adalberta Alberti Fidanza, and in collaboration with Giovanni Ferro Luzzi and Marcello Proja. The nurses received specific training in diet assessment before the start of the study and surveyed subsamples of men in three different seasons between November 1959 and January 1961. These nurses did a wonderful job collecting information from all members of the families to which the sampled men belonged. In the chapter on Dietary Surveys, more details will be given about this aspect.

In the spring of 1962 Flaminio Fidanza and Bruno Imbimbo, re-examined 888 subjects in Crevalcore and 573 in Montegiorgio. With the help of Pier Luigi Mattioli of Naples we recorded, on a random sample of 155 men of Montegiorgio, a blood glucose tolerance test, serum cholesterol, and haemoglobin. In spring 1963 and in 1964, Bruno Imbimbo started collection of data on mortality and causes of death and morbidity, recording at the same time ECG tracings on subjects suspected of having cardiovascular conditions.

Srecko Nedeljkovic (left) and Alessandro Menotti (third left) during fieldwork, Montegiorgio, 1965

In the spring of 1965 we carried out the 5-year re-examination on all survivors of the cohorts in Crevalcore and then in Montegiorgio. Altogether 874 men were examined in Crevalcore and 662 in Montegiorgio, then aged 45 to 64. During the same survey, data on food intake were collected in all men, using the dietary history method. Men belonging to the original subsample surveyed in 1960 underwent another dietary survey conducted by the weighing method, based on three days intake. In Crevalcore, headquarters for the second survey was located in the foyer of the local theatre. Meanwhile, the municipal guard, Ivo Donini, had died, and Alfonso Barbieri invited all subjects to be re-examined. In Montegiorgio examinations were again held in the town hall and Egidio Marziali, municipal clerk, joined Guerrino Allessandrini for recruitment of subjects.

The basic field staff included Flaminio Fidanza from Naples as coordinator, Alessandro Menotti, cardiologist from Rome, Bruno Imbimbo, internist from Naples, Ignazio Mazzuca, cardiologist from Rome, George Lamm, cardiologist from Budapest, Srecko Nedeljkovic, cardiologist from Belgrade, Josef Pokorny, cardiologist from Prague, and Robin Herron from Northern Ireland who recorded apex cardiograms. In addition, Hans Friedrich and Herman Wolf, both engineers from Munich, guided by Pentti Rautaharju from Helsinki, recorded ECGs on magnetic tape for further computer analysis. Anthropometry and other measurements were assured by a group of clerks and technicians. Major international participants were Ancel Keys and Henry Blackburn from Minnesota.

At the end of 1965 Flaminio Fidanza moved from Naples to the University of Perugia as full Professor of Nutrition and Food Science, while in early 1967 Bruno Imbimbo was appointed in a large pharmaceutical industry. As a consequence, a large part of the coordination of the study was taken over by Alessandro Menotti of the Center for Cardiovascular Diseases of the St. Camillo Hospital in Rome. He also became responsible for collection of morbidity and mortality follow-up data. This proved an excellent choice, since Alessandro Menotti had been trained in epidemiology and medical statistics at the London School of Hygiene and Tropical Medicine in 1964, and again in 1967, and had participated in the fieldwork of the Rome Railroad cohort in 1962 and in others in Dalmatia, Crevalcore, Montegiorgio, Crete and Corfu between 1963 and 1966.

In 1970 the 10-year follow-up survey was characterized by the presence of a large team of about 20 persons. The group of clinicians and cardiologists from Rome was helped by a large staff of nutritionists sent from Perugia and by an international group again led by Pentti Rautaharju, then from Halifax, Canada, for the magnetic tape recording of resting and exercise ECGs, apex-cardiograms, and carotidograms. Again, George Lamm from Budapest provided great help, thanks to his skill in Italian. The other cardiologists on duty in the field were Paolo Dini, Giuseppe Messina, Paolo Signoretti, all from Rome, and Josef Pokorny of Charles

University in Prague. On that occasion, examinations were again held in the usual season, in a partially empty shirt factory in Crevalcore (guarded by a statue of a crocodile watch dog), and in the municipal offices in Montegiorgio, where there was a high participation rate (93.3%).

All the serum cholesterol measurements and food composites were analyzed in Naples at the beginning of the study, and later in Perugia, taking care of all the Italian and Yugoslavian cohorts, and part of the Greek ones. The collection and coding of mortality data shifted in 1970 at the end of central U.S. funding and in the study's economic crisis. Coordination continued due to the position of Alessandro Menotti as Research Associate at the Laboratory of Physiological Hygiene, University of Minnesota and his new appointment in Italy.

A gap in continuation of the study was created by the retirement of Vittorio Puddu from his hospital position in 1976 and by changes in the institutional duties of the Center for Cardiovascular Diseases of the St. Camillo Hospital of Rome. The appointment in 1979 of Alessandro Menotti as chief for chronic diseases at the Laboratory of Epidemiology and Biostatistics of the Istituto Superiore di Sanità in Rome (the National Institute of Public Health), re-opened the possibility to proceed, with the whole project incorporated into the official programs of the Institute, and with Alessandro Menotti as principal investigator. Partial funding from the Istituto Superiore di Sanità and grants from the European Community (mainly for the study of water characteristics in relation to heart diseases), and from the Italian National Research Council, allowed us to resume and complete the mortality follow-up and to organize re-examinations of the original cohorts in 1980 (20 years of follow-up), in 1985 (25 years), and in 1991 (31 years).

Important roles in this more recent phase were played by Bruno Giuli, mainly for the field organization in 1980 and 1985; by Simona Giampaoli, who little by little took over responsibility for training personnel for quality control of the procedures, and finally also for organization of the field work, and by Gino Morisi, for the biochemical measurements made from 1980 onwards at the Istituto Superiore di Sanità. Flaminio Fidanza and Adalberta Alberti Fidanza continued to handle the dietary aspects of the study. Among the cardiologists who helped with the fieldwork were Salvatore Panico from Naples, assistant to Mario Mancini and also former fellow at the Laboratory of Physiological Hygiene, and Paolo Emilio Puddu, nephew of Vittorio Puddu.

Survey examinations were held in 1980 in the premises of local schools, both in Crevalcore and Montegiorgio; in 1985 in the Local Health Unit in Crevalcore and in a school in Montegiorgio; and in 1991 in local hospitals in both places. Again, participation rates were high (79% in 1980; 76% in 1985, and 67% in 1991) in spite of the increasing age of the subjects and the fact that many of them had changed residence.

In 1980, 1985, and 1991, it was necessary to start, each time, new negotiations

with the local Administrative and Health Authorities, due to the time gap between 1970 and 1980 and to the frequent changes in responsible people (and political parties) in the local administrations. The acceptance of the proposed examination was always good. Locally we exploited the fine cooperation from the municipal guards and population register officers. In 1991 an important organizational contribution was made in Crevalcore by Giorgio Luppi, medical officer of the Regional Health Service of Bologna.

In 1985, for the first time, substantial additions were made to the original examination protocol (which had always been preserved) by including questionnaires on mental depression and self-sufficiency which were felt to be appropriate in dealing with an elderly population (then aged 65-84). This represented a pilot experience in expansion of the objectives of the study, moving from the classical cardiovascular risk factors, prevalence, incidence, and mortality, to interest in the physical and functional status of the elderly and their prediction. This operation was later conducted jointly with the Dutch group, led by Daan Kromhout, for the cohort of Zutphen, and with the Finnish group, led by Aulikki Nissinen, for the East and West Finnish areas.

The whole plan was developed through cooperation among the three national groups; a large number of tests and questionnaires targeted at the description of depression, self-sufficiency, mental state, and physical functions was developed, tested, and standardized and then applied to all men in the 30th-anniversary reexamination in Finland (1989), in the Netherlands (1990), and on the 31st anniversary in Italy (1991).

In the 1991 field examination in rural Italy, assistance was also obtained from Edith Feskens of the Dutch team, who took care of blood glucose, hemostatic, and other biochemical measurements, and of Paula Kivinen of the Finnish group, who supervised functional tests. Simona Giampaoli was fully responsible for the field operations in 1991 and was co-principal investigator in the 'elderly part' of the study. Other physicians participating in the fieldwork in 1980, 1985, and 1991 were Giuseppe La Pera, Gisella Faggioli, Antonio Parma, Michele Matano, Giuseppe Cigna, and Roberto Amici.

Two other important operations were carried out in the 1980s. Between 1985 and 1988 a complex and extensive data gathering system was established by Alessandro Menotti in the two survey communities. It provided the date of each major coronary and cerebrovascular incident event that had occurred during the first 25 years of follow-up. In this way a large number of events were identified which, for several reasons, were not completely ascertained from procedures of the quinquennial surveys and routine collection of mortality data. For the major coronary events, in particular, about 50 more cases of definite non-fatal myocardial infarction were added to the about 250 found through the original system. The greater completeness in

Fieldwork team and some participants in Crevalcore, 1991.

incidence data improved current analyses.

In 1987 the Italian group participated, under the guidance of the Dutch group led by Daan Kromhout, in the collection of food composites from local markets, attempting to represent the average food intake of each cohort in the Seven Countries Study at the time of the entry examination. This was done both in Crevalcore and in Montegiorgio, and then extended to Rome for evaluation of the diet of the Railroad cohort. The major role in this field activity was played, on the Italian side, by Simona Giampaoli, with the help of Annemarie Jansen of the Dutch group.

Conclusions

The rural Italy section of the Seven Countries Study represented a milestone in cardiovascular epidemiology in Italy and set a number of precedents. It was the first true epidemiological enterprise on population samples in the country, providing prevalence, incidence, and mortality figures on CHD at short and long term follow-up. For years these were quoted as the only such data available in Italy. The study is presently still underway, and is the oldest and the longest in Italy in terms of follow-up. It was the first study in Italy to show the relationship there of the classical risk factors to CHD events and the first to provide multivariate analyses on CHD and other end-points such as cerebrovascular disease, other causes of death, and all-

cause mortality. Analyses identified risk factors for single diseases specifically in contrast to those predicting several causes of death and all-cause mortality. Again, the data set of the Italian cohorts has been the basis for new procedures evaluating risk factor changes over time as predictors of cardiovascular events, which were then applied to other cohorts of the Seven Countries Study.

Data collected by dietary history contributed largely to definition of the so-called 'Mediterranean diet', and more recently have been the first employed for definition of dietary patterns, in contrast to analysis of single foods or nutrients, and for study of their relationship to different causes of death and total mortality.

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8

STUDIES ON THE ROME RAILROAD

A. Menotti

The Seven Countries cohort known as the Rome Railroad was enrolled in 1962 to represent the counterpart of the U.S. Railroad cohort already studied in the late 1950s. My participation in the Italian group provided a person fully dedicated to the Seven Countries project and to cardiovascular epidemiology. My previous experience was working as an internist and cardiologist at the Government Hospital of Tripoli, Libya. There I 'discovered' epidemiology for myself, observing the different mix of morbid conditions, mainly cardiovascular, on hospital wards in Tripoli compared to Rome. I measured the blood pressure of all in-patients, out-patients, accompanying relatives of patients, and household dwellers because of an impression that blood pressure was lower in Libyans than in Italians.

From 1962 I received, as unpaid assistant at the Center for Cardiovascular Diseases and Division of Cardiology of the St. Camillo Hospital in Rome, the label of 'epidemiologist' from Vittorio Puddu, despite lack of formal training in the discipline. After early experience with the Rome Railroad cohort, I took over responsibility for the Italian section of the study. In a few years I became the responsible person for all three Italian areas of the Seven Countries Study, establishing an Epidemiological Unit within the Center for Cardiovascular Diseases of Rome.

Negotiations for the activation of the Rome railroad cohort had been started in 1961 by Vittorio Puddu, with the cooperation of representatives of the Italian Institute of Social Medicine, by involving the Directorate of the Medical Service of the Italian State Railroad attached to the Ministry of Transportation. Both the management and the trade unions were well informed and motivated toward the study and eventually allowed enrollment of a sample of men working in Rome and surroundings. A key role was played by Mario Monti, then Deputy Director and later Director of the Railroad Medical Service, since he fully understood the scientific potential of the operation, together with the possible 'fall-out' for the Medical Service itself in terms of the possible establishment of routine screening for cardiovascular risk factors and diseases. The Railroad Study in Rome was supervised by Henry Taylor of the Minnesota team who was, at the same time, principal investigator for the U.S. Railroad cohort.

The sample in Rome was based on identification of railroad employees in specified occupations (station masters, switchmen, electricians, and maintenance-of-way men) working in the Department of Rome of the Italian State Railroad system. Actually this department included not only the city of Rome but almost all the region around Rome (Lazio), the southern part of Tuscany (north-west), and part of Abruzzi (south-east of Rome). About half of the identified men were living in the metropolitan area of the capital and the other half in small centers up to 150 km from Rome. Fortunately, the subgroup living out of Rome never showed any differences from the others except for the greater difficulties in organizing their follow-up for vital status, mortality, and causes of death. The work in Rome was greatly helped by other persons whose role is acknowledged here: Vittorio Puddu acted as principal investigator, together with Mario Monti of the Railroad. Aldo Bellini, a psychologist working in the Medical Department of the Railroad, was the key person in the general organization. Mario Mancini of Naples, one of the early fellows of the Laboratory of Physiological Hygiene, had the responsibility to train the medical staff, including Alessandro Menotti, Bruno Floris, Piero Marroni, Luigi Struglia, plus some nurses of the railroad. Flaminio Fidanza, from Naples, took responsibility of treating the blood samples before mailing them dried to Minneapolis.

The survey operations, organized in the First-Aid Rooms of the Stazione Termini, the main rail station in Rome, were held in May, June, and part of July 1962, and completed in October of the same year. In spite of the organizational difficulties in working schedules of railroad employees and appointments for examination, the participation rate was acceptable, finishing with more than 80% and a total of 768 men.

All subsequent operations, consisting of follow-up for vital status, mortality and causes of death, became the full responsibility of Alessandro Menotti with the patronage of Vittorio Puddu, the organizational help of Mario Monti, and the assistance of Flaminio Fidanza for the nutritional aspects, in which a subsample of men was studied in 1969, using the seven- day diary technique.

The 5- and 10-year survey re-examinations of the rail cohort were held in the out-patient section of the Center for Cardiovascular Diseases of the St.Camillo Hospital in Rome and in the Medical Service of the Railroad, with teams enrolled among the medical and nursing staff of the Hospital and the Medical Service of the Railroad. The physicians cooperating on these two occasions were Bruno Floris, Ignazio Mazzuca, Alessandro Nardelli, Francesco Ceccherini, Giuseppe Lobefaro, and Paolo Signoretti. The two examinations took place in the late spring of 1967 and in the fall of 1972, respectively. The latter survey, in particular, gave a number of difficulties in obtaining a reasonable participation rate in relation to the distance of men's residences (mainly for those living outside Rome), the conflict between the working schedule, the appointments, and the fact that many subjects had retired in

Henry Taylor and Vittorio Puddu during fieldwork, Rome Railroad, 1962

the meanwhile because of special benefits offered for early retirement. In 1967 the Rome team was again bolstered by the direct supervision of Henry Taylor of the University of Minnesota.

The period between 1973 and 1979 was characterized by the end of central funding from NIH for field operations beyond the 10th-anniversary survey and by economic difficulties bound to the international oil crisis. It was impossible for the Rome group to get funds for a 15-year re-examination which would in any case have been unrealistic in view of achieving a high participation rate. In fact, more and more subjects had retired and moved out of Rome to their original birthplaces. Mortality follow-up activities were thus interrupted until 1980, well beyond the 15th anniversary (1977).

In 1979 Alessandro Menotti moved to the Laboratory of Epidemiology and Biostatistics of the Istituto Superiore di Sanità in Rome (the National Institute of Public Health of Italy). Thanks to funding and facilities obtained from the Institute, and a grant from the Italian National Research Council, it became possible in 1980 to resume the rail cohort follow-up for vital status and causes of death. The task was particularly difficult despite continued help from the Medical Department of the Railroad. In any case, the collection of data covered 15 years follow-up (corresponding to 1977), and then the 20- and 25-year deadlines corresponding to 1982 and 1987. The job was finished in 1989 and due to many difficulties was never considered likely to reach the 30-year follow-up, as for the two Italian rural cohorts.

The study in Rome could, nevertheless, be compared usefully with the U.S. stu-

dy of railroad employees. Clear-cut differences were shown between the two groups: the group with higher levels of blood cholesterol and cigarette smoking in the U.S., and slightly higher levels in Body Mass Index and blood pressure in Rome. The 5- and 10-year follow-up showed a definitely higher (about two-fold) CHD incidence and mortality in the U.S. group compared to the Italian, partly explained by differences in cholesterol level and smoking habits.

Within the Rome cohort, different incidence and mortality from CHD were found among subgroups characterized by different amounts of physical activity at work, with higher rates among those with more sedentary jobs. In a recent analysis it was shown that the 25-year all-causes mortality in the Italian Railroad cohort was definitely lower than that in the rural Italian areas combined (about 20% less). This was not the case, however, for CHD and lung cancer, which had similar rates in the railroad to the rural men. Finally, all-causes death rates, adjusted for risk factors unrelated to occupational exposure, made the difference drop to a non-significant 12%, removing any possible 'healthy worker effect'.

There were two important 'fall-outs' from the Rome rail cohort study. The Directorate of the Medical Department of the railroad took the opportunity, from the success of the operation, to offer a voluntary screening program to the employees, which went on successfully for several years until the mid-eighties when the whole organization of the Italian railroad was completely changed, including the role of the Medical Department. On the other hand, Vittorio Puddu and Alessandro Menotti, thanks to the excellent relationships developed with the Medical Department, could, in 1973, draw a new sample of men aged 40-59 from the Rome Railroad (and from the Ministry of Transportation). This was then studied for many years within the Italian Section of the WHO European Multifactor Preventive Trial of CHD in industry.

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9

STUDIES IN THE GREEK ISLANDS

C. Aravanis and A.S. Dontas

It was in the fall of 1954 when one of us (CA) met Ancel Keys and Paul White during the second World Congress of Cardiology. The discussion centered around the differences in frequency of coronary and other heart diseases in various parts of the world. One of the topics discussed was the reputedly low prevalence of coronary and other heart diseases in Crete compared to most other parts of the continent, and the way of life and diet of Cretans, which differed in many respects from those of urban Athenians or northern Europeans. This discussion was continued by both of us during a meeting of the Research Committee of the American Heart Association in Chicago, one year later.

At that time evidence had started to accumulate on the large differences in coronary heart disease existing between populations living in widely separated parts of the world. These differences, on the order of 5 to 1, had been known to exist between Europeans and native Africans, but it was a relatively unexpected finding that within Europe, Finns and southern Europeans could have differences almost as large. The difficulty in estimating more accurately the magnitude of these differences led to the decision to study specific population groups in southern Europe to determine these prevalences with some precision in well-defined and demographically stable areas.

Crete had already been studied in 1947-1949 by a group of scientists from the Rockefeller Foundation as a 'case study of an underdeveloped area' in Europe. It had suffered a savage war during the 1941 German attack to occupy it, and subsequently during an active guerilla war in the effort to establish a free area. This culminated in the capture (and subsequent evacuation to Egypt) of the commanding officer of the German forces on the island, General Kreipe, by a team of British-Greek commandos.

In a large flat, wooded area 30 km southeast of Herakleion (Ancient Kandia) the German forces had created amidst the olive trees a large airstrip for ammunition storage and as a fueling station for their activities in the Middle East. This area and all villages nearby had very little contact (one winding country road) with Herakleion and the other large cities on the coast. The inhabitants for generations led a frugal life which had barely differed from that of their ancestors. It was decid-

ed, therefore, to study the 13 villages surrounding the plain. Preparations for a field study started early in 1957 and the local authorities, in particular Dr. G.E. Hadjakis, health commissioner and Dr. E. Staphylakis helped by lending the ambulance of the commission to carry equipment and personnel. Mr. G. Arnaoutakis, driver and liaison person, was always of great help.

Meanwhile, between October 6 and November 1, 1957 the first pilot survey of the Seven Countries Study, of 598 men, took place in Nicotera, a village some miles north of Reggio di Calabria in south Italy. The place still bore marks of the Second World War, with many houses and roads in need of repair and children bearing clinical signs of malnutrition, i.e., underweight, rickets etc.

A number of interested scientists from various parts of the world, as well as the two co-authors of this section, were invited for a 2-day conference in Gioia di Tauro, Calabria, at the start of the survey. The experience obtained in this exploratory survey was quite satisfying, and the Greek counterpart of the pilot study was carried out in the county of Kastelli Pediada in Crete between October 22 and November 24 the same year on 657 men, aged 45-64. Dietary records and samples were collected under the guidance of the veteran dietary scientist, Helen Sdrin, between October and the end of December 1957.

For this work, the sum of U.S.$2,000 was provided by Dr. Keys, and some additional funds were contributed by the ELAIS olive-processing industry in Athens. This covered travel expenses from Athens and back for the group (Ancel and Margaret Keys, Dr. P.D. White, Dr. Noburu Kimura, Dr. J. Carlotti, Dr. F. Fidanza, Dr. M. Karvonen, Drs. Aravanis, Costis and Cybele Chlouverakis, Dontas, and Helen Sdrin), the Herakleion Astir hotel costs, and the daily travel costs from Herakleion to the villages of Pediada and to the Venizeleion Hospital, where the food samples were homogenized and stored.

Transportation of the group was secured in the Plymouth station wagon of the Keys' family and the Austin ambulance of the health commission in Herakleion. These were loaded very early each morning and driven over primitive roads to the villages. There was no hotel in Kastelli nor in any of the villages in the area. Running water was scarce and electric power was practically absent; thus, a generator had to be used for operating all scientific equipment.

The field difficulties were astounding: on days following a rain, roads to the villages were impossible, and the Plymouth from Minnesota had to be helped by avant-marchers who removed large stones from its path. Due to delay in transport of Sanborn Visette paper from the U.S.A., ECG paper was in such short supply that Margaret Keys and Noburu Kimura spent the evening hours cutting ECG paper lengthwise and rewinding each half on used axles. Most of the group collected fleas and other insects during the physical examinations and spent some time each evening in de-infestation.

The results of these two pilot surveys were, nevertheless, amazing: only four cases of myocardial infarction were found in Nicotera and two in Kastelli: in similar total population samples in the U.S. at least fivefold greater frequency would have been expected. The diet was also quite peculiar; more than 40% of total calories were derived from fats, 29% of calories were monoenes of oleic acid, 7% were saturated fatty acids and 3% polyenes. It was not uncommon to see farmers start their working day by drinking a cupful of olive oil, topping it off on cold days with 'tsikoudia', a strong spirit made from grapes.

Unfortunately, the data from this study, despite the above findings, could not be used as a basis for international comparisons and long-term follow-up. The clinical records were too sketchy; only one out of every five men had serum tested for cholesterol, and the lack of ECG recording paper made exercise testing rare. Further, respirograms, carotid pulse tracings, and urine tests were not obtained. Finally, the consensus of the other groups was that the populations studied should be composed of 40-59 year-old men rather then of 45-64 year- olds. Thus, after long deliberations it was decided to repeat the study later in the same area and add another Greek population with similar diet but a more 'western' way of life.

Application for a grant-in-aid was sent to the National Heart Institute in June 1959, some months following a similar 'group' application from the collaborating centers from Finland, Italy, Dalmatia, Slavonia, and Serbia. The Greek application (H-5037, Nutr.) included a request for funds to cover a similar population in Corfu, where the level of development and economy was much higher than in Crete; the application also included a request for a full dietary survey on the two islands.

Unexpectedly, this application was not approved by the National Heart Institute, for reasons not clear, even today, but presumably from the reviewers' impression that a prevalence study had already been done, and that a second one in the same area would not add much more information. The Italian application, following similar unsatisfactory field experiences in Nicotera, was modified so as to study two villages, Crevalcore in northern Italy and Montegiorgio in central Italy, grossly differing in their diet; it was approved.

In the fall of 1959 and the spring of 1960, after the negative outcome of our first try, another application was sent to the U.S.P.H.S. for a study of the same area of Crete and a similar one in Corfu; the latter included seven villages around Corakiana, some 15 miles north of the capital, Kerkyra. Although the area was chiefly rural, almost one-third of the men were sedentary or engaged in the tourist industry. The application, submitted by the Hellenic Society for the Study of Atherosclerosis, included plans to study, in addition to the main cohort of 40-59 year-olds , smaller cohorts of 80-100 men aged 25-28, and 70-74 years, in each area. This application (HE-06090) was approved by N.I.H. In the interim, the then Royal Hellenic Research Foundation had approved grants-in-aid to the two co-authors

here which could be used for epidemiological study in the two areas; a number of individual donors and the Elais Oil Company in Greece (the late V. and L. Melas) also contributed various sums for this study. Doctors A. Keys and P. White helped significantly in realizing these funds. Later grants were obtained from the International Olive Council, the E.E.C. and the Greek Association of Industries and Processors of Olive Oil (SEVITAL).

Thus, in the fall of 1960 the 3-year re-survey of the Cretan population, aged 40-59, became the entry survey of the modified Cretan cohort (686 subjects) and the following year the same age groups of the Corfu cohort (529 subjects) were similarly studied.

These two cohorts had some peculiarities compared to the Italian, Croatian, or Serbian cohorts: the populations were scattered in small villages; thus, to obtain the maximum response rate the entire team and equipment had to be transferred from village to village every few days during the survey. The very poor and hard-working Greek farmers would not consent to be examined away from their villages. The help of the local doctors and various local authorities was of immense importance in securing, finally, a very high rate of participation; in addition, a member of the Greek team was functioning as a goodwill person to convince doubters of the need to be examined and, once examined, have the rest of their families examined as well!

Paul Dudley White, Christ Aravanis, Ivan Mohacek reading ECG's, Crete, 1960

Transportation of the group between Herakleion and the villages was secured this time with a pick-up truck, generously loaned by the U.S. Air Force base in Herakleion (Col. John Sheen) who also placed a driver at our disposal (the largest unexpected grant-in-aid our group received during the 1960 survey).

The 1960 group included as new members Doctors. D. Lekos, A. Corcondilas, D. Galanos, C. Vasilikos, G. Stamatoyanopoulos, M. Tzelisi, M. Papadatou, and others from the Greek side, Dr. Alessandro Menotti with his bride Maria-Luisa, Dr. B. Imbimbo from the Italian side, and Dr. Henry Blackburn from the U.S.A.

The difficulties encountered in the field study in Corfu were even worse than in Crete: there were no laboratory or hospital facilities remotely comparable to those of the Venizeleion hospital in Herakleion, and all laboratory work had to be done in the village centers, with small rooms and no running water or electric power. The number of subjects working in the Corfu tourist industry had increased in previous years and made recruitment of the last 10 to 15% of the subjects an enterprise as frustrating as chasing butterflies. The costs of prolonging the stay of the staff so as to include the last doubters in the survey were very high for the Corfu surveys, and the coverage obtained at each resurvey was lower than in Crete. We are, however, very grateful to the men and to the local authorities of Crete and Corfu, whose early and continued cooperation made this great study feasible and successful.

The five, 10, 15, 20, 25 and 30-year follow-up surveys on the two islands became progressively easier in technical details (transportation, recordings, local analyses) but more difficult in recruitment of the hesitant subjects, especially for Corfu.

In the interim years, the collection, reviewing, coding, and processing of mortality data and causes of death was carried out by the same principal investigators, assisted by physicians mostly from Professor Aravanis' Department of Cardiology. Doctors Paul Ioanides and Adrian Corcondilas, two U.S.-trained cardiologists, were of immense help; of great assistance also were Doctors. J. Steriotis, E. Papasteriades, J. Ktenas, and N. Karalias. The team included cardiologists, dietitians, lab people, and helpers who visited the two islands at regular intervals. With the cooperation and help of local physicians, community authorities and others, rosters were reviewed, and the cause of death was discussed, evaluated, and verified. A visit or direct communication with the hospital authorities took place for all deaths.

In 1979 a Joint Meeting with the investigators of the Seven Countries Study was held in Heraklion, Crete. Papers were presented by the Seven Countries investigators: C. Aravanis, A.S. Dontas, A. Keys, H. Blackburn, D. Kromhout, A. Menotti, H. Toshima, B.S. Djordjevic, and S. Nedeljkovic. Data from related studies were shown by J. Stamler, Z. Pisa (WHO) P. From-Hansen, G. Tibblin, L. Wilhelmsen, I. Balaguer-Vintro, J. Pobee, and D. Kozarevic. During the meeting many new ideas were developed for future follow-up studies and data analyses.

Publication of Greek data has been slow because of the lack of central analytical facilities and scarcity of funds. Nevertheless, interesting reports have appeared over the years, including findings not directly connected with coronary heart disease; numerous follow-up reports are in preparation.

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10

STUDIES IN CROATIA

R. Buzina

My introduction to cardiovascular research was in the fall of 1950 when I joined the Institute of Biochemistry of the University of Basel as a postgraduate fellow in biochemistry and vitaminology. Professor Karl Bernhard, then the Director of the Institute, proposed a couple of themes for my research activities. The one I found most interesting was to study the effects of deuterium-labelled dietary cholesterol on the development of coronary atherosclerosis in rabbits. Unfortunately, it turned out that the concentration of the label was insufficient for quantitative analysis, and the results were never published. On the other hand, I became interested in the problem of diet and atherosclerosis, and became quite familiar with the current research on that subject.

At that time it was already recognized that though the level of serum cholesterol could not serve as a reliable criterion of blood vessel integrity in individuals, it was found useful as an index of the so-called atherogenic potential in population studies. The observed differences in blood cholesterol in the early studies were related primarily to the amount of fat in the diet. However, in 1952 Kinsell and co-workers, and shortly afterwards, Keys and co-workers found significantly lower levels of serum cholesterol when vegetable fats were fed isocalorically than with the fats of animal origin in the diet.

These data were of great interest to us, and we decided to investigate how these results of relatively short experimental studies would compare with the mean cholesterol level in populations living on different amounts and types of fats practically for generations. Opportunities for such an epidemiological study presented themselves in 1953 when Dr. Josef Brozek from Ancel Keys Laboratory came to Zagreb on sabbatical leave, also providing a small grant which enabled us to plan the study.

Three regions of Croatia were selected for this study. One was the region of Osijek in eastern Slavonia, characterized by a high animal fat intake (98 g/capita/day). The second region was in the Dalmatian hinterland and characterized by a low fat intake, mainly of animal origin (44 g/capita/day).The third region was an Adriatic island where olive oil represented 90-95% of all fat used in the household. The average fat intake was 118 g/capita/day of which 85 g was olive oil.

The mean serum cholesterol level differed markedly between the regions. In the area where over 90% of fat intake was of animal origin, the level of serum cholesterol, standardized for age, was 239 mg/100 ml (Bloor method), but only 211 mg/100 ml in the 'low fat' region where fat intake, mainly of animal origin, was less than half that of the other region. The lowest serum cholesterol level, however, was found in the 'olive oil' region. Despite the fact that total fat intake was the highest, the serum cholesterol level was 201 mg/100 ml, the lowest of all three regions (1).

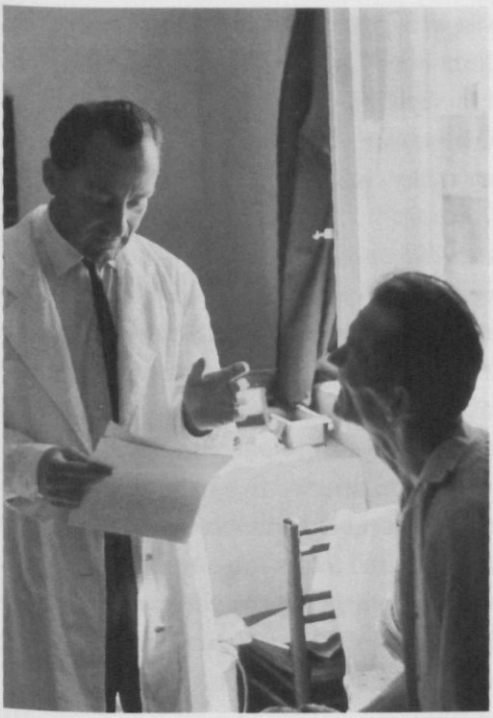
I had the chance to discuss these data with Dr. Keys during a study he organized in 1954 in Naples, and we agreed that it would be interesting to expand this study and to investigate the prevalence of CHD in the examined regions of Croatia. Though no final plans were developed at that stage, during my stay in Naples I had the privilege to meet and work with Italian counterparts, Professors Fidanza, Bergami, and Mancini and also with members of Dr. Keys' team, including Mrs. Margaret Keys, Dr. Henry Blackburn, Dr. J.T. Doyle from Albany, N.Y., and Mr. Ernst Klepetar from Minneapolis. During our work in Naples we had a chance to meet the 'elite' of world cardiologists headed by Dr. Paul White, including Professor Vittorio Puddu from Rome, Professor Oliver from Edinburgh, Dr. Jacques Carlotti from Paris, Professor Gunnar Björk from Gothenburg, and distinguished researchers from Finland, Professors Paavo Roine, and Martti Karvonen.

The stay in Naples was an excellent introduction to the epidemiology of CHD. A year later I was invited by Dr. Keys to spend one year as a research fellow in his laboratory in Minneapolis where, besides other things, I also took part in his follow-up study of CHD in Minnesota business and professional men.

During this time Dr. Keys became interested in the effects of fats on the blood coagulation system. So I introduced and modified techniques for measuring components of the blood clotting mechanism, the results of which were quite interesting; the same amount but different types of fats affected the whole blood clotting time to various degrees, as well as the conversion of prothrombin to thrombin (2,3).

After I returned to Zagreb in late 1956, contacts were established with a number of people interested in research on CHD in the U.S.A., Italy, Finland, Greece, and Japan. In 1957 Dr. Keys was able to secure central funds for a collaborative study on the epidemiology of CHD, and was instrumental in enabling Professor Fidanza and myself to obtain NIH grants for studies in Italy and Croatia. (Due to the very short time left to meet the NIH deadline, Dr. Keys sent for both of us to come to Rome, where we prepared the protocol for the study practically in one day, sitting on a bench amidst the colorful spring flowers and the singing birds of a beautiful Roman park.)

In the fall of 1957 a field trial to test the protocol, methods, and organization proposed for the Seven Countries Study was carried out in the village of Nicotera near Reggio Calabria in southern Italy. Most of the key persons in the long-term study



Ratko Buzina and a subject, fieldwork Dalmatia, 1958

from England, Finland, Japan, The Netherlands, Greece, and the U.S.A. took part in this pilot study.

The experience from the Nicotera study enabled us to refine the protocol and methods, and develop logistics for the follow-up study. In early 1958 we started selecting populations in predominantly 'animal fat' or 'vegetable fat' areas. To keep responsiveness of the population as high as possible and to strive for near-zero loss during follow-up, it was decided to select men of rural areas, who were less likely than urban men to change occupation, habits, and/or residence. The target was to include about 700-800 subjects aged 40-59, in each cohort.

In the 'animal fat' area for Croatia we selected four villages in the region of Osijek in eastern Slavonia, including the village where the 1953 pilot study was carried out. The villages were quite homogenous in regard to diet and occupational activities, and what was very important, the population, as well as local authorities, were very cooperative and interested in the study.

In the 'vegetable fat' area, however, there were not enough subjects of the required age on the island of the 1953 study, and we had to organize a rapid screening of the food intake pattern of much larger populations along the Dalmatian coast. Eventually about 12 villages and hamlets strung along 60 km of the coastal area in the region of Makarska were selected.

The formal study was initiated in Dalmatia in September 1958 and in Slavonia at the end of October. The response rate was quite high. Of 684 subjects included in the roster of Dalmatia, 671 (98.0%) attended the field clinics. There anthropometric, clinical, biochemical, and electrocardiographic examinations were carried out. The vital capacity (FEV), as well as ballistocardiography, were included in the examination.

In Slavonia, from 732 included in the roster, 696 or 95.0% of subjects were examined. The reason for a relatively lower response in Slavonia was the temporary absence from the area of a number of subjects, not uncommon at that time of the year when agricultural activities were less intensive. However, health certificates were obtained from local physicians for all absent persons.

During the 1958 field study, parallel dietary surveys were initiated. Twenty-four families in Dalmatia and 25 families in Slavonia were selected in a random process from the list of heads of families included in the clinical examinations. Food consumption was recorded for seven consecutive days. All foods eaten by the families and by individual heads of the household were weighed, and the volume of beverages except water measured. Quantitative duplicates of all foods except alcoholic beverages and water were collected, as consumed, to make a seven-day food composite for chemical analysis. Detailed menus and recipes were also recorded, and at the end of the week the totals of each foodstuff were computed for each participant. Corresponding portions of those foods were purchased locally to make up equivalent composite aliquots. These equivalent composites were homogenized, lyophilized, sealed under nitrogen, and sent for analysis to the laboratories in Minneapolis and Naples. The dietary studies were repeated in 1960 and 1961, and results published together with similar data from Finland, The Netherlands, Italy, and Greece (4-6).

The clinical, anthropometric, and biochemical examinations were repeated in 1963 and 1968, and the results of these findings were published in a number of journals and in the three major Seven Countries monographs. They are well known and will not be repeated here.

The baseline study, as well as the follow-up studies in Dalmatia and Slavonia, were carried out by international teams with the participation of experts from other countries included in the Seven Countries Study. This opportunity was utilized to organize international seminars on the epidemiology of coronary heart disease, in which other prominent scientists, including representatives of WHO, participated. In the view of Dr. Paul White these gatherings played an important role in breaking down barriers to international scientific cooperation in Europe, then still divided by the Cold War.

After 1968 the 10-year follow-up survey in the study in Croatia was concentrated on the collection of morbidity and mortality data. The financial situation did not

permit the clinical and biochemical re-examination of all subjects included in the original roster, but subjects with elevated risk factors were examined subsequently on several occasions. After 1980, however, only data on mortality were collected.

The 25-year mortality follow-up was made possible through a grant of the Netherlands Nutrition Foundation to Professor Kromhout. The collection of mortality data was carried out under the supervision of Professor Mohacek by special teams of senior medical students. On the basis of house-to-house visits, they collected information on deceased subjects originally enrolled in the study, including documents relevant to the cause of death. Death certificates were collected and additional information was sought from local physicians and/or the hospital, in the case of hospital treatment.

During the collection of mortality data invaluable assistance was given by the local health services. Information on the health status, and in case of death, death certificates, were obtained for subjects who emigrated to faraway countries such as Australia, Chile, and Canada. After 25 years of follow-up, mortality data were obtained from 98% of the originally selected roster. This was most rewarding for all colleagues and members of the local health services involved in the study.

After the 25-year follow-up the Slavonian cohort had a very high mortality rate. The difference in mortality was primarily the result of difference in CHD deaths (ratio to other area 1.8) but also in the ratios of all-causes death (1.5) and cancer death (1.2).

During the 25-year span of the study, members of the core field team were practically the same. Among those, Professor Mohacek was responsible for electrocardiographic and clinical examinations and Professor Marinkovic, with the assistance of Dr. Smetisko, was responsible for clinical work. With regard to dietary examination, most of the work was planned and supervised by Professor Ferber and Dr. Branka Tiefenbach-Agneletto, and later by Dr. Anna Brodarec. Dr. Agnes Horvat prepared food composite samples. But equally important was the contribution of a number of people instrumental in setting up a highly competent field team and directly supporting the logistics of the field operations. Among them were Professor Arpad Hahn, then director of the medical clinic of the University of Zagreb and his successor Professor Radosevic. Professor Vugrincic, former chief of the medical department of the Osijek general hospital and Dr. Marinovic, director of the primary health care center in Makarska. They secured the best possible cooperation between field teams and the local primary care personnel in Slavonia and Dalmatia, respectively. Without the assistance of these and local authorities it would not have been possible to complete the study so successfully.

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11

STUDIES IN SERBIA

S.I. Nedeljkovic

Early in the 1950s there was some 'talk' in Belgrade about the epidemiology of chronic mass diseases, including cardiovascular diseases (CVD). Epidemiology at that time, in health services and academic institutions, dealt primarily with communicable diseases. After the Second World War, in 1945, the most prevalent disease was pulmonary tuberculosis (TBC), a consequence of deficient housing, extensive migration, food shortages, underdeveloped health services (with shortages in essential medicines), primitive communication systems, etc. A special TB Institute was founded and a widespread net of dispensaries organized throughout the country. Other infectious diseases were epidemic, too: typhus (typhus exanthematicus), typhoid and paratyphoid (Salmonellosis), hepatitis, dysenteries, tetanus, diphtheria, poliomyelitis, plus endemic malaria and syphilis. A huge hospital for infectious diseases had been in operation for years in Belgrade. In Internal Clinics A and B there were many cases of rheumatic fever and valvular heart disease, as well as infectious endocarditis. In rural areas chronic bronchitis was prevalent, in most cases a sequel of pulmonary tuberculosis, or other non-specific, repeated bronchial or pulmonary infections.

By the late 1950s, however, there were more and more cases of angina pectoris and myocardial infarction crowding the hospitals and clinics. At the Third World Congress of Cardiology in 1958 in Brussels, Čedomil Plavšič presented a report (with myself a co-author) on coronary heart disease in Yugoslavia (YU), which was later published in Acta Cardiologica, showing the upward trend in coronary heart disease (CHD) in many parts of the former YU. Professor Plavšič, a well-known YU cardiologist, soon moved to Abazia (Opatija) on the Adriatic coast to organize a CVD Rehabilitation Center - Talasoterapija.

The late Professor Božidar S. Djordjević (1910-1986), a scholar of the French cardiological school and student of the well-known cardiologist, Camille Lian, instituted in the Internal Clinic B two wards for cardiovascular patients and formed a professional cardiological team. In 1965 he founded postgraduate cardiology training at the Medical Faculty in Belgrade. He then sent younger associates abroad for additional training. Vladan Josipović was among the first to spend time in London,

San Francisco, and the Twin Cities of Minnesota during 1958 and 1959, and he was in touch with teams already working in CVD epidemiology. I got a certificate in biostatistics during six months training at Columbia University, New York, in 1961 and, by coincidence, was assigned a thesis on the epidemiology of CHD!

Seven Countries Study Connections

Early in 1961 a meeting was held in Zagreb (Croatia) with participation of Ancel Keys, Ratko Buzina, Ivan Mohaček, Radovan Ivančić, Božidar Djordjević, and Vladan Josipović, where plans for a Serbian Seven Countries Study (SCS) were considered. In June 1961 Ancel Keys participated in the third YU Congress of Cardiology in Opatija, lecturing on the 'Risk of CHD', and summarizing the first results obtained in the International Cooperative Study he had already started in Croatia, Italy, Finland, Japan, the U.S.A., and Greece (Crete). Invitations had been sent to Božidar Djordjević and Vladan Josipović to join the SCS, and to come in September to Corfu and take part in field surveys conducted by Christ Aravanis and Anastasios Dontas from Athens University. In Corfu the Minnesota standards, methodology, and protocols were agreed upon with Ancel Keys, and the decision made to conduct the Serbian SCS.

Serbian SCS Beginning Organization

Professor Djordjevic was then quite influential as Chief of Cardiology in Internal Clinic B, and also as Pro-rector and soon-to-be Rector of Belgrade (BG) University, as well as Director of the Serbian Institute for Medical Research. He enthusiastically organized the Serbian SCS, getting a broad range of support. Clinical examinations of subjects in the Serbian SCS were covered in different phases of study, by Vladan Josipović, Chief of Cardiology after Djordjević's retirement, Ivan Lambić, later Chief of Cardiology in another hospital, Gradomir Stojanović, Chief of Cardiology after my retirement, Ljubica Božinović, Chief of the Coronary Care Unit for more than 20 years before retirement, Miodrag Ostojić, now Chief of Cardiovascular Diagnostics and Interventional Cardiology, Miodrag Grujić, Chief of Arrhythmology in the Institute of Cardiovascular Diseases (ICVD), and Dejan Bošković, Chief of Cardiology in ICVD.

Thomas Strasser was given the delicate laboratory work of preparation of sera on filter papers to be sent to Minneapolis for central determination of serum cholesterol, a variable considered of primary importance in the SCS. Dr. Strasser was with the Serbian Study until 1969, when he moved to Geneva to become medical officer in the Cardiovascular Disease Branch of WHO. He also spent 1965 in Minneapolis in the Laboratory of Physiological Hygiene (LPH), helping to code and sort data of the three Serbian cohorts. He was the first to publish data on diabetes mellitus in

the Serbian cohorts, encouraging endocrinologists from Internal Clinic B to continue that optional study over 25 years. In 1962 he spent three weeks in Rome participating in the Rome Railroad study group, and his contribution to the Serbian Study was essential to the entry and fifth-year field surveys.

Božidar Simić, a highly reputed nutritionist with experience in the relations between diet and CVD, had previously published a paper on that topic concerning Serbia before he joined the cardiological team. With his associate, Arsenije Simić, he trained students to record the food intake of 41 men in Velika Krsna (VK) in October 1962 and May 1963, of 44 men in Zrenjanin (ZR) in September 1963 and November 1963, and of 41 Belgrade University professors in February 1964. With the help of nutritional chemist, Šibalić (Belgrade), and of the laboratories in Naples (Flaminio Fidanza) and Minnesota (Ancel Keys), data on energy intake, protein, carbohydrates, and fats (including fatty acid profile) were obtained in seven-day food duplicates. We realized, of course, that diet had priority in Ancel Keys' approach to the epidemiology of CHD. In the beginning, however, most of the Belgrade clinical staff was curious about the name of the institution which Ancel Keys and his staff represented, the 'Laboratory of Physiological Hygiene' (LPH). The guiding idea soon became obvious: a laboratory with an interest in research into the physiological aspects of lifestyle, with diet as the central point. The name has since been changed to the Division of Epidemiology (1984). But I still feel nostalgia for the old name, LPH *(a nostalgia shared by the editors).*

From the very beginning I was, in my role of fieldwork organizer, personally responsible for ECG recordings and codings, and mortality follow up. After 1975, when professor Djordjević retired, I received full responsibility for the Serbian CVD Study. I had several nice opportunities, because of Ancel Keys' help, to join field surveys with Martti J. Karvonen's team in West Finland in 1964 and Alessandro Menotti's team in Montegiorgio, Italy in 1965.

The Serbian CVD Study got overwhelming acceptance from all professionals involved in the study: clinicians, cardiologists, nutritionists, technical staff, administrative personnel, the subjects, as well as community support from all levels. The examinees were not treated as objects of experimentation, but given a full report and counsel on their health, with freedom to return for medical check-ups if necessary. They used this opportunity often, especially in Belgrade. The reputation of the SCS was such that it was possible to get grants from various research agencies; from 1970-1973 NIH Special Foreign Currency PL-480, 02-033-1 support was vital to carrying out the 10-year follow-up surveys and tracing vital status of all men entering the Serbian cohorts in 1962-1964.

SCS Continued

After the third round of fieldwork to collect 10-year data, there was a lull in Serbian and SCS activities between 1974 and 1982. Field surveys beyond 15 years were omitted (1977-1979), except for mortality follow-up. In 1980 Ancel Keys published his capital book 'Seven Countries. A Multivariate Analysis of Death and CHD', indicating the need for further follow-ups, for getting more information on the power of classic CHD risk factors and their change over time, and factors related to life expectancy. Critical decisions were made during the meeting of the SCS Steering Committee at Heraklion in Crete, September 1979, organized by Christ Aravanis with Ancel Keys and Henry Blackburn, and all principal investigators present. It was decided to raise personal funds for further continuation of individual components of the SCS. The new principal investigator of the Dutch study, Daan Kromhout, who took over the Zutphen Study after the death of F.S.P. van Buchem, gave impetus to the international cooperation. He was later of great help for the Serbian part of the SCS, directly participating in field surveys in 1987 (VK), 1988 (ZR), and 1989 (BG), with his assistant Bennie Bloemberg. He continued research on the baseline dietary data by analyzing fresh food composites for nutrients, fatty acids, and dietary cholesterol, with the help of Professor Martijn Katan from Wageningen, The Netherlands. He also took sera of participating survivors in three Serbian cohorts for measurement of the lipid profile.

Velika Krsna (VK), 1962

VK is a typical Serbian village spread over hills and streams in the region called Forestland (Šumadija), with a surface area of 15 x 15 km, 250-300 m above sea level, inland about 30 km south of the Danube river, and about 70 km from Belgrade. Farmland is interspersed with forested hills, grasslands, fruit orchards, (plums, apples, pears, peaches), and vineyards. In 1962, when the VK study started, the village was interconnected by small macadam roads, with one road leading to the nearby town of Mladenovac, 15 km away, and to Highway Belgrade-Niš. In 1967, during the second survey, there was a paved road connecting Mladenovac and the main Highway, through VK. VK has a small center with a large community building, in which the examinations took place, as well as a church (Greek Orthodox), an elementary school, a health station (opened in 1966), a veterinary station, a few taverns, and small shops. The village has about 5,000 inhabitants, 90% farmers with small farms and limited cultivating machinery. Some youngsters are employed in nearby Mladenovac, connected by a regular bus.

The climate is continental with four typical seasons, sometimes with heavy snow and rain, but also with very dry weather in July and August. Nearby attractions are a renovated 'Spa Selters Mladenovac', and Topola-Oplenac, a place with a hotel and

monastery (Greek Orthodox) known as a 'mausoleum' of Karadjordjević's monarchy, and the tomb of the last Yugoslav King, Alexander, killed in Marseille in 1934. This place was visited by most of the foreign guests participating in the SCS.

The cohort in VK consisted originally of 706 men, but for later SCS analyses only 511 were included because those aged 35-39 and 60 or more were considered 'out of age'. The population of VK was stable and only a few men migrated to the nearby towns Mladenovac or Smederevo, since the majority of examinees owned private land, houses, cattle and poultry farms, or small farming machinery. Most of the foods, even alcoholic beverages, were home made, and diets were rich in bread, milk, cheese, eggs, pork, lamb, and chicken. Fish was only occasionally used, mostly during the religious fasting periods before Christmas and Easter, holidays more observed in the villages than in the towns. In local shops salt, oils, sugar, beer, candies, textiles, and technical goods were on sale. The examining study staff enjoyed excellent local hospitality and luncheons with homemade food and drink.

At the baseline examination 96.7% of the men aged 40-59 participated in the study. The entry examinations at VK were supervised by Ancel and Margaret Keys, and Henry Blackburn, who introduced ECG recordings and an 'Outline of suggested criteria for clinical diagnosis in population studies'. All data obtained in VK were put into special Minnesota forms and soon shipped to Minneapolis for analysis .

Among the standard examinations, an optional radio-iodine thyroid uptake was carried out in a subsample by the team of Professor Peter Milutinović. Significantly higher uptake rates were observed for the VK cohort compared with the ZR and BG University cohorts examined in 1963 and 1964. A possible explanation for the subjects in VK could be higher physical activity, lower body weight, lower sum of triceps and subscapular skinfolds, and the lowest entry serum cholesterol level of all SCS cohorts (mean 160 mg/dl).

The other 'optional' study was carried out by a group of pulmonologists who recorded spirometric findings during 25 years of follow-up. About 20% of the subjects in VK had impaired lung function, a significant predictor of subsequent mortality from bronchitis (mostly as a sequel of previous lung tuberculosis), and cor pulmonale.

It was relatively easy to track vital status and causes of death of men in VK who entered the SCS in 1962. This was due to the availability of a local death certificate service, Health Station documentation, nearby hospital records (Mladenovac, Smederevska Palanka, Belgrade), and the excellent help of the local physician, Slobodan Imširagić and cardiologist Milan Andjelković, who did his thesis on the causes of death in VK. We had in VK a very good contact person, Petar Vulićević, who was for many years official clerk of the local community and knew every man there; he was himself a participant in the VK study. He died recently from hypertensive vascular disease, Parkinsonism, and stroke.

During the whole SCS we had wonderful cooperation with ophthalmologists looking for changes in the oculi fundi: Professors Dobrica Cvetković, Dušan Stojanović (died in 1978), and Siniša Djaković. They published a few papers on ophthalmologic findings in the journal 'Serbian Archive'.

Another ancillary study done repeatedly on subjects of the Serbian SCS was testing the value of Dock's direct body ballistocardiography in epidemiological surveys. Abnormalities of ballistocardiography were significantly more prevalent in older age and in men with hypertension, obesity, and impaired lung function. The results were presented in an International meeting on ballistocardiography and have been published.

Zrenjanin (ZR), 1963

As a contrasting population with a different environment and lifestyle, an Agroindustrial Combine (AIC) 'Servo Mihalj' in the town of Zrenjanin was selected as the second Serbian cohort in the SCS. Zrenjanin is situated 70 km north-west of Belgrade, across the Danube river. It is typical of the province of Vojvodina (area Banat) and the cohort probably deserves the more appropriate name 'Vojvodina'.

ZR surroundings has 22 villages, with 81,316 inhabitants living in the town in 1991, 136,778 in the region in all, with many ethnic groups (25), but mostly Serbs and Hungarians, and some Romanians and Slovaks. The territory is flat, with rich farming land, bordered by the great rivers, Danube and Tisa, a smaller one, Tamish, and the Begej River, running directly through the center of Zrenjanin. There are a few lakes and places for fish breeding (Echka carp stews). There is also a water irrigation system, the Danube-Tisa-Tamish-Danube canal. An abundance of vegetation and forestry creates opportunities for hunting ducks, pheasants, and rabbits; fishing in the rivers is excellent.

Out of 5,000 workers employed in AIC 'Servo Mihalj', a roster of men above age 35 was established, and a total of 720 men examined at entry in September 1963. A response rate of 98% was achieved. After elimination of younger and older men, 516 men, aged 40-59, remained for follow-up in the SCS. The ZR cohort is composed of 253 Hungarians, 239 Serbs, 17 Romanians, and 7 Slovaks.

After 25 years of follow-up, ZR's cohort reached nearly the top of SCS age-adjusted CHD and stroke death rates, 181/1000 and 119/1000, respectively. There were no ethnic differences, except for the small group of Slovaks, with 6 deaths out of 7 examined at entry. In the ZR cohort the mean levels of serum cholesterol (mg/dl) increased from 169 in 1963 to 207 in 1968, and 230 in 1973. From ZR's cohort we learned the epidemiological lesson that people in Vojvodina are at very high risk for CVD, partly through an unhealthy lifestyle and a diet rich in animal fats as main risk factors, although causal explanations are far from being clear cut.

The SCS team enjoyed an enthusiastic welcome at 'Servo Mihalj' during 25 years of cooperation, although the industrial cohort was the one most difficult of the three Serbian cohorts to trace in the long run. Retirement of workers, and migration all over former YU and abroad, caused large problems, with at least 15 men lost to follow-up. By good luck we had a friendly and helpful contact man, social-welfare worker Danilo Babic, employed with 'Servo Mihalj' for more than 30 years and always at hand. He did all mailing and inquires on the whereabouts of men entered into the SCS cohort in 1963. There was also a renovated hospital in ZR, city central office for vital statistics, and a helpful physician employed at 'Servo Mihalj' Health Station. Having AIC automobiles at our disposal, we made many visits to the examinees and the disabled in town, as well as in the villages.

Belgrade University Professors (BG), 1964

Belgrade University professors were chosen on the insistence of the Serbian members of the SCS, pointing out differences between intellectual and physical occupations. The difference was especially large between University persons, with a sedentary lifestyle and peasants in VK, engaged in heavy physical activity. Except for a few administrators at the University, all examinees were professors or lecturers in 16 faculties. All professors engaged in the Serbian SCS also entered into the BG cohort, and all are alive today except Professor Djordjević, who died from stroke in 1986, having suffered from CHD.

Srecko Nedeljkovic (second right) supervising the exercise step test, Belgrade, 1964

The BG response rate for entry examinations was 85% of all professors at the University, aged 40-59 in January 1964. However, the overwhelming response of 239 subjects, aged 40-44, brought the mean age of the cohort of 538 men down to 47.8 years, the lowest mean age of all cohorts in the SCS. The initial number of BG subjects was 654, but after elimination of younger and older persons, 538 were included in the SCS cohort. Though the selection of the BG cohort has been criticized, and the cohort left out of many analyses, looking back after 30 years, we were fortunate with the BG group. On subsequent 5-year examinations response rates were between 80-85%, and there was no trouble following vital status of all entry men. Each year a book of University staff affiliation was edited with addresses and phone numbers. It was also possible to obtain the necessary information from the administration, especially for retired professors. Most professors use health services at the University Clinical Center and Institute of Cardiovascular Diseases (ICVD). Many who survived or died from CHD were treated at the Coronary Care Unit of the ICVD. The daily newspaper 'Politika' regularly publishes obituaries and photographs of deceased persons, which also helps track BG professors.

At entry BG professors had higher levels of BMI, sum of skinfolds, serum cholesterol, and CHD prevalence than men in VK and ZR. During the first 10 years of follow-up, they were at higher CHD risk. However, after 25-years of follow-up, the ZR cohort reached the highest total for CHD and stroke mortality. The 25-year all-cause mortality rate of BG professors was 347/1000, lowest among all 16 cohorts of the SCS. Protective factors might have been the higher educational level of the select population, better socio-economic status, and health behavior resulting, for example, in a low percentage of cigarette smokers after 25 years of follow-up. Also, there was easier accessibility to health services, a factor which has not been specifically measured in SCS and could have played a role in reducing mortality risk.

Finally, I would like to close with some remarks on Belgrade today. Belgrade is a metropolitan, international city of about 1.5 million inhabitants, the capital and administrative center of the former and new YU, and has been developed and enlarged during the last three decades. Except for the outskirts and the industrial region of Rakovica, 'dirty' industries have been kept far outside the city. Being an important political and military strategic point, Belgrade was heavily destroyed several times during World War II and in past wars between the Austro-Hungarian and Ottoman Empires. After World War II, many people entered the city, producing an immense population growth. Until recently, housing has been a major problem, but in the last decade intensive construction and stimulation of private property has coped with the shortage.

Belgrade and suburbs are situated on the right bank of the Danube and on both banks of the Sava river junction with the Danube. Both rivers are polluted by upstream industries, with chemicals endangering the quality of the water supply.

Smogs are occasional, usually shortlasting and cleared by 'koshawa', a north-east wind coming along the Danube from the Karapati mountains in Romania.

Belgrade is supplied by an extensive commercial network of food chains, as well as by many farmers 'green' markets offering fresh produce. There are many parks suitable for recreational physical activities as well as for gardening, which is popular among intellectuals. There are also beaches on the Danube and Sava, with one very popular beach, 'Ada Ciganlija', having a crowd of more than 100,000 people daily during the summer months.

Collaboration with Alessandro Menotti

One of those who proved most helpful in the Serbian CVD Study, and who participated in all field surveys from the beginning, was Alessandro Menotti, whom Ancel Keys placed as coordinator of the European part of SCS. Following European cohorts of the SCS, he was stubbornly insistent on complete SCS data and built in Rome, in collaboration with Ancel Keys and Rose Hilk in Minneapolis, a Master Tape of SCS data. In 1979 he moved from the Cardiology Department at the St. Camillo in Rome to his place in the Laboratory of Epidemiology and Biostatistics, Istituto Superiore di Sanità, dedicating much time to SCS and analysis of SCS data, including the Serbian part. His appointment as Director of the Laboratory of Epidemiology and Biostatistics in 1990 did not change his attention to the SCS and he continued the 25-year follow-up analyses, as well as having responsibility for nine organizational units and a staff of 150 people. The last time he visited Belgrade was in 1989, during the 25-year follow-up examinations of the University professors. Later, in 1989, I took the opportunity to visit his Laboratory in Rome, where he provided me the tape with data of the Serbian cohorts.

Collaboration with George Lamm

The Serbian Study was connected with the Hungarian Study started in 1965 by George Lamm and Ivan Gyarfas. After both of them moved to WHO, the Hungarian study did not achieve long-term follow-up. George Lamm participated in the field examinations in Velika Krsna in 1972 and Zrenjanin in 1973; I had met George Lamm earlier during the fieldwork of the Italian cohort in Montegiorgio in 1965.

In February 1971 I had the pleasure to drive Margaret and Ancel Keys from Belgrade to Szeged and back to Belgrade for a visit to the Hungarian field survey, including the nearby villages, Szekkutas and Martely. Ancel Keys intended to extend the Seven Countries Study to the Eight Countries Study! It was a pity that those data could not be included in the SCS. One would expect similar findings and

CVD trends as in the Serbian Zrenjanin cohort since nutrition, geography, geology, climate, and socio-economic conditions are approximately the same in the two areas.

Collaboration with Henry Blackburn

Henry Blackburn was passionately involved in the Serbian SCS from the very beginning until 1972, when he became Director of the LPH after Ancel Keys' retirement. His responsibilities were extended later, when the LPH was transformed into the Division of Epidemiology of the School of Public Health of Minnesota, to running a faculty of 40 and a staff of more than 600 employees. His support of the SCS was encouraging during the meeting of SCS principal investigators in Crete 1979, when he had to leave the meeting abruptly because of the urgent brain operation on his son in the U.S.A.

Henry Blackburn made his appearance in Velika Krsna in 1962, helping with ECG recording and Minnesota coding. He is the author of the widely accepted Minnesota Code, an ECG classification system so needed in epidemiological studies of CVD. The Minnesota Code is an indirect characterization of the cardiovascular health of populations, and predicts future morbidity and mortality events. Later he formed a central SCS coding office at the LPH. The Minnesota Code procedure was technically developed to the point that even technicians could make reliable measurements and coding of all ECG items. In 1963-1965 he made an appeal to all colleagues engaged in ECG recordings and codings in field surveys to criticize the Minnesota Code to improve it and avoid ambiguities, and reduce intra- and inter-observer variability. To overcome these problems, all ECG tracings from the Serbian SCS were shipped to Minneapolis for central reading and coding, and for clinical classification of 'hard' and 'soft' CHD. The code was then modified in the WHO Manual on Cardiovascular Survey Methods in 1968.

We were then stimulated to buy ink-writing ECG machines (Elema-Schönander, Sweden) with higher frequency response, instead of cheaper direct ECG writers. An exercise test was adopted for field examinations with a step 30 cm high to be climbed and descended 60 times per 3 minutes under metronome pacing.

In 1967 (VK), 1968 (ZR), and 1969 (BG) a new project was introduced in the Serbian SCS by Doctors Blackburn and Rautaharju: magnetic tape recording of the conventional ECG, orthogonal XZY leads, and bilateral carotid and femoral pulses (at rest, during exercise, and in recovery). Everything sounded very attractive to me as a cardiologist. Ancel Keys wrote about the idea, mentioning 'large costs might be involved, but if you could arrange and help we will be in favour'. The idea was costly: new equipment, engineers, customs problems, adjustment of electricity in villages, transportation, personnel, etc. For the Zrenjanin field survey in 1968 we waited, together with Henry Blackburn, at Belgrade airport several days before all

the equipment came, prolonging work a few days in order to get an adequate subsample of examinees.

Nevertheless, everything went off in orderly fashion, according to Henry Blackburn's suggestions (letter on August 21, 1967): 'I would suggest that the test be a progressive one so that the older or more disabled subject would not be overstressed at the onset and provide warm up ... a short instruction session of pedaling against no resistance and optimal adjustment of the height of the bicycle seat (Monarch static bicycle) ... This would be followed by a two-minute warm-up at 50 watts, two minutes at 100 watts and two minutes at 150 watts, with an end heart rate of 130-140 bpm, and three minutes for the recovery period'.

This idea was realized with excellent engineers from the Dalhousie University Department of Physiology and Biophysics, Nova Scotia, Canada, under the logistic guidance of my acquaintance from the Finnish field survey in 1964, Professor Pentti M. Rautaharju. His associate, now professor, Herman K. Wolf, was 15 days with us in Velika Krsna in 1967, and John Scherwood for three weeks (for the cohorts in Zrenjanin) in 1968, and for the Belgrade University professors in 1969. The other person active in this field, doing the same work in Finland, Italy, and Croatia, was Ing. Hans Friedrich from Munich, whose visits I recall with gratitude.

I got a pleasant letter from Herman Wolf in 1990: 'We have pulse waves from Yugoslavia and Japan, and a combination of one pulse wave and heart sounds from Italy ... It is our intention to explore the pulse wave velocity as a predictor for long-term blood pressure evolution and event rate prediction.' Of course, I approved.

Another sparkling idea was proposed by Henry Blackburn in a letter to me (July, 1972) recommending studies of 'hygienic treatment of premature ventricular beats using physical activity, stopping smoking, reducing alcohol and coffee, improving sleeping habits, versus drugs'. As a clinically minded cardiologist, he tended to do both intervention and observational epidemiological studies *(Eds.-but that 'sparkling' experiment yielded no clear results!).*

Collaboration with the Group of George Kozarevic

In the 1980s joint efforts were made to obtain funds for the continuation of the Serbian SCS as well as the "Yugoslav Cardiovascular Study", led by George Kozarević with associates Nikola Vojvodić, Jasenka Demirović, and Živorad Račić. The Yugoslav Cardiovascular Study, in progress from 1964-1965 until 1988, was carried out with Framingham Study protocols in consultation with Doctors Dawber, Gordon, Zukel, McGee, Schenker, and Kaelber. Field surveys in the three Serbian cohorts were conducted jointly with Kozarevic's group in the period 1982-1989, enabling 20 and 25-year follow-up studies of the survivors and collecting information on causes of death.

International Meetings and Seminars

Important for the Serbian SCS were the meetings of the Research Committee of the International Society of Cardiology in Makarska, Dalmatia in September 1963 and in Venice, Italy in April 1965 under the chairmanship of Ancel Keys. Topics covered issues of methodology and feasibility of epidemiological studies of CVD in free-living populations. At that time Paul Dudley White was actively promoting research in preventive cardiology and organizing international cardiological foundations. In the Fifth World Congress of Cardiology in New Delhi in 1966, he became the first President of a new cooperative International Society of Cardiology, still in existence under the name International Society and Foundation of Cardiology (ISFC). Ancel Keys became the first Chairman (1966-1970) of the Section on Epidemiology and Prevention of the ISFC. That Section with its Council, is still very active in World Congresses of Cardiology and the International 10-Day Teaching Seminars.

The methodology of CVD epidemiology was discussed in extenso during a WHO meeting held in Moscow in 1965, with participation of D. Ried from London, Z.Piša from WHO, G. Lamm from Budapest, A. Mjasnikov, E. Chazov, I. Glazunov and A. Ahmeteli from Moscow, and myself. Most of the ideas developed in the SCS were supported with calls for more intensive research and cooperation.

In 1968, an annual 10-Day International Teaching Seminar was first given in Makarska and continues until today, held in many places all over the world, offering younger students systematic training in the epidemiology and prevention of CVD. I attended the second in Pioppi in 1969, using the occasion to participate in a meeting of the Steering Committee of the SCS held at Keys' home, "Minnelea", in Pioppi. Two associates of the Serbian SCS attended 10-Day International Teaching Seminars: Dejan Bošković in Hungary, (Estergon) in 1972 and Miodrag Ostojić in Ghana (Accra) in 1977. Ostojić also participated in the Advanced 10-Day Teaching Seminar in Singapore in 1993.

Meetings of SCS Members at Zrenjanin and Belgrade in 1985

An important stimulus to the Serbian study was a get-together of SCS investigators, headed by Ancel and Margaret Keys, and the Belgrade Serbian Academy of Science and Arts in Zrenjanin in November 1985. The first symposium in the Agroindustrial Combine (AIC) 'Servo Mihalj' was on 'CVD and nutrition'. Round table discussions were participated in by Ancel and Margaret Keys, Daan Kromhout, Alessandro Menotti, Annemarie Jansen, Frederick Epstein (Zurich), Ratko Buzina, Božidar Simić, Srećko Nedeljković, George Kozarević, AIC technologists Erne Schvan, Dušan Radaković, Miodrag Zotović, and Savo Ivančević. These discussions included results of nutritional studies related to CVD in the SCS, as well as considerations of nutritional products of AIC 'Servo Mihalj' in Zrenjanin. A booklet of AIC prod-

Srecko Nedeljkovic, Alessandro Menotti and Daan Kromhout at meeting of the Serbian Academy of Science and Arts, Belgrade, 1985

ucts was enclosed for the discussion, with detailed composition of nutritional items. Technology of their production was presented to the participants.

AIC 'Servo Mihalj' was enlarged and intensively developed following World War II from a plant originating more than two centuries ago in former Austro-Hungaria. The firm controls a large food market in Yugoslavia and abroad, especially meat, sugar, beer, fruit products, pharmaceuticals, and cosmetics. AIC also produces cereals and starch products, many sorts of bread, doughs, desserts, dishes, pastries, ready-made pies, biscuits, marmalade, and margarines. Four different edible oils are produced: sunflower seed oil 'Dijamant', soybean oil, rapeseed, and corn germ oil 'Evit'. Rapeseed oil is rich in oleic acid, 50-74%. Sunflower seed oil, soybean oil, and corn germ (maize) oils are rich in linoleic acid, up to 60% of all fats, with 0% peroxides. Among diary products they produce 3.2% pasteurized cow's milk, sheep's sour milk, different sorts of yoghurt, butter, and a variety of cheeses.

All these products have been shown and tasted on several occasions by our epidemiologic research team, and were broadly discussed during the Zrenjanin meeting in 1985 with an international faculty. It was concluded that there is more work

to be achieved by the food industry in the search for a healthy diet. On that occasion, two books were brought to the attention of the audience and presented to the 'Servo Mihalj' library: 'Eat Well and Stay Well' (edited in 1959 and 1963) and 'The Benevolent Bean' (edited in 1967 and 1972), written by Margaret and Ancel Keys. In the library of 'Servo Mihalj' there are also all monographs, and many reprints, edited by Ancel Keys and other SCS authors.

The second symposium was held on November 8, 1985 at the Serbian Academy of Science and Arts (SANU) with the help of the Secretary of the Medical Unit of SANU, Academician Vladimir Kanjuh, Professor of pathology, who, after the death of Academician Djordjević, provided further grants for the Serbian part of the SCS. The title of the symposium was 'Twenty years of epidemiological investigations of CHD in Serbia. The Seven Countries Study'. Ancel Keys presented a paper on 'Diet and 15-year death rate in the SCS', which was later (1986) published in the American Journal of Epidemiology. Alessandro Menotti presented 'CHD risk factors evaluation in the Italian part of the SCS', Daan Kromhout, 'Fish consumption and CHD in 20 year follow-up of the Zutphen Study', and Srećko I. Nedeljković, Vladan Josipović, Božidar Simić, Vladimir Slavković, Gradomir Stojanović, and coworkers, different aspects of the Serbian study of the SCS. Ratko Buzina and Ivan Mohaček showed results of research on 'Risk factors in adolescents in Croatia'. George Kozarević and associates presented different aspects of the 'Yugoslav Cardiovascular Study'. Frederick Epstein from Zurich reviewed the topic 'Prevention of CHD: status and perspectives'. President of SANU, Dušan Kanazir, reported his research on 'Psychosocial factors in CVD and cancer', pointing out the importance of the 'Rationality/emotionality index' as a risk factor. Sorely missed at the meeting of SANU was Academician Božidar Djordjević, founder of the Serbian SCS, due to severe illness from which he died soon after, in 1986.

Summary

The three Serbian cohorts, first examined between 1962 and 1964, were the last to enter the SCS, already in progress since 1958, not counting numerous pilot studies before that year. The cardiological team of Belgrade Medical Faculty, led at that time by the late Professor Dr Božidar S. Djordjević, founder of the Serbian SCS, enthusiastically accepted the idea to join an International Cooperative Study on Epidemiology of CVD. After a few meetings with Ancel Keys, founder and coordinator of the SCS, professor Djordjević and Vladan Josipović were invited to attend field surveys conducted by Christ Aravanis in Corfu 1961, and to adopt the same methodology and protocols for forthcoming studies in Serbia. Some of the cardiologists were already trained abroad, mostly in the U.S.A. (Vladan Josipović, Srećko I. Nedeljković, Toma Strasser, George Kozarević, *et al.*), and were becoming familiar

with cardiovascular epidemiology and prevention. Božidar Simić was engaged for the nutritional part of the Serbian study . He was already known through research on diet and CVD in some areas of Serbia.

In a search for contrasting populations three Yugoslav cohorts were selected: a village, Velika Krsna, 70 km south-east of Belgrade, a food processing plant in the town Zrenjanin (Vojvodina) 70 km north-west of Belgrade and across the river Danube, and Belgrade University intellectuals. Thus, three social classes were represented: farmers, workers, and academics.

Over many years numerous international exchanges of colleagues were realized to ensure rigorous standards necessary for an international cooperative study: central planning, reliable measurements, data-base construction, sophisticated analyses, and publications. Valuable international help to the Serbian SCS was afforded by Ancel and Margaret Keys, Alessandro Menotti, Henry Blackburn, Daan Kromhout, and others. Before writing this report, I arranged two entire books of correspondence taking place over the 30 years of our joint endeavour!

Of 2,080 men examined at entry in three Serbian cohorts of the SCS, 1,563 have been followed; the cohorts were limited to the age classes 40-59 at entry: 511 men from VK, 516 from ZR-Vojvodina, and 536 from BG University. Overall age-adjusted mortality in 25 years was highest in Vojvodina (577/1,000), intermediate at VK (497/1,000), and lowest in BG University (347/1,000), probably explained by higher socio-economic status and better health behavior in professors versus farmers and workers. CHD risk factor increases over time were greatest at ZR, especially blood pressure and serum cholesterol, leading to the highest 25-year CHD death rate of 177/1000 in ZR vs. 122/1,000 in VK, and 118/1,000 in BG University.

The mortality follow-up of the Serbian cohorts of the SCS will be continued. However, turmoil in the former Yugoslavian territories is creating more new health problems and human disasters, requiring different types of epidemiological and preventive research, and public health action.

Acknowledgments

The following persons played a central role in realizing the Serbian part of the Seven Countries Study:

Božidar S. Djordjević, (1910-1986), internist, cardiologist. Chief Investigator SCS Serbia until 1986, Director of Institute for Medical Research, Chief of Cardiology in Internal Clinic B, Pro-rector and Rector of University Belgrade. Professor of Internal Medicine and Cardiology of Medical Faculty Belgrade (MFB).

Vladan Josipović, (1920-), retired 1985, internist, cardiologist. Chief of Department of Internal Medicine, Professor of Internal Medicine and Cardiology of MFB.

Toma Strasser (1922-), cardiologist, Professor of Balneoclimatology of MFB. Since 1969 Medical Officer Cardiovascular Diseases WHO, Geneva.

Srećko I. Nedeljković (1923-), internist, cardiologist. Director of Institute of CVD Belgrade, Director of Cardiology in Internal Clinic B. Professor of Internal Medicine and Cardiology of MFB. Since 1986 Chief Investigator of the Serbian part of the SCS. Chief of Postgraduate Cardiology 1980-1989.

Božidar Simić (1920-), medical doctor, nutritionist. Head of Nutrition Department, Serbian Institute of Hygiene of MFB.

Ljubica Božinović (1924-), internist, cardiologist. Chief of Coronary Care Unit 1970-1989 in Internal Clinic B. Professor of Internal Medicine and Cardiology of MFB.

Gradomir Stojanović (1929-), internist, cardiologist. Chief of Third Cardiology Department and Coronary Care Unit. Professor of Internal Medicine and Cardiology of MFB. Chief of Postgraduate Cardiology since 1989.

Vladimir Slavković (1922-), Professor of Internal Medicine and Pulmology of MFB, Chief Editor of Serbian Archive of Medicine.

Miodrag Č. Ostojić (1946-), internist, cardiologist. Chief of Diagnostics Department on ICVD, Belgrade. Associate Professor of Internal Medicine and Cardiology of MFB.

Miodrag Z. Grujić (1944-), internist, cardiologist. Chief of Arrhythmology Department on ICVD, Belgrade. Associate Professor of Internal Medicine and Cardiology of MFB.

Nikola M. Vojvodić (1934-), Professor of Internal Medicine of MFB. Director of Institute of Gerontology and Home Care, Belgrade.

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12

STUDIES IN RURAL JAPAN

H. Toshima

The story of the Seven Countries Study in Japan begins with the late Professor Noburu Kimura, who died of acute leukemia in 1983. Only he could provide details of the beginning of the Japanese study cohorts. Therefore we will cite a short essay that Professor Kimura wrote in 1971, describing his close friendship with Dr. Keys.

My Friendship with Dr. Keys

'It was in the fall of 1954, or 18 years ago from now, when I first met Professor Ancel Keys, who later became a leading researcher of the well-known epidemiologic survey called 'Seven Countries Study'. I was invited to a symposium of the Second World Congress of Cardiology, entitled Epidemiology of Atherosclerotic Heart Disease. In the symposium, I planned to present the pathological data of coronary atherosclerosis of the Japanese, based on examining 2000 autopsied hearts that had been stored in Kyushu University. The data were completed through the efforts of the members of the cardiology laboratory in the First Department of Internal Medicine, Kyushu University.

On the way to attend the congress, I visited the University of Minnesota, where I had stayed for 6 months, 2.5 years earlier, to ask my friends there for stylistic correction of my English presentation. They were all electrocardiologists, so they recommended that I consult with Professor Ancel Keys who was also an invited speaker at the same symposium. Although he was very busy preparing for his own presentation, he was kind enough not only to correct my English but also to renew my slides. His kindness greatly contributed to my very successful presentation in the Congress.

In 1955, the following year, I enjoyed the second meeting with Professor Keys, when I attended the first assembly of the Expert Committee of WHO in Geneva, representing Japan. This reunion brought us the opportunity to discuss a plan for our future collaborative study. Our idea came from the consensus in the previous symposium that revealed much less frequency of coronary arteriosclerosis in

Japanese as compared with U.S. Caucasians. The difference could offer a key to understand underlying mechanisms for the development of atherosclerosis. Four months later in March 1956, Professor Keys visited Fukuoka, together with Professor Paul D. White and Professor Bronte-Stewart. We extended our idea and reached an agreement to conduct a collaborative study on Japanese men in their forties, including employees working in a Shime coal mine, farmers residing in village of Koga, and medical doctors practicing in private clinics in Fukuoka.

In the following year, 1957, we participated in the international collaborative surveys conducted in southern Italy and Crete, Greece. Professor Keys and I were assigned to carry instruments for the survey, driving a station wagon from Rome to Nicotera, which is located in the tip of the boot-shaped Italian Peninsula. On the way, we stayed one night in a motel, where we had the unforgettable experience of being the victims of a robbery. We were very upset to see all the recording papers for the electrocardiograms were stolen.

We both participated in various subsequent surveys in Italy, Yugoslavia, and so on. I still remember that we took a pleasant stroll in several towns connected with Baroque music, our common pastime, in Viennese and Cremona in northern Italy for a few days. Shortly afterwards I was hospitalized, and had a surprising visit from Professor Keys in Fukuoka to inquire about my health after hearing a rumor that I was suffering from lung cancer (which was fortunately incorrect and proved to be lung abscess). And still today we are personal friends and professional associates.'

The Period 1958-1976

Tanushimaru and Ushibuka men were selected for the Japanese cohorts in the Seven Countries Study for the following reasons: *1* the first criterion was stability of the population that seemed important to assure success of the long-term follow-up; *2* the second criterion was the availability of local physicians who understood the importance of the study and were willing to support it. Professor Kimura had a special interest at that time in whether dietary protein intake correlated with the incidence of cerebrovascular attacks, particularly cerebral hemorrhage, and therefore selected possible contrasting cohorts, Tanushimaru and Ushibuka. Tanushimaru was a farming town, located in the suburbs of Kurume, where the traditional Japanese diet was maintained, with calorie intake largely depending on rice. In contrast, Ushibuka was a fishing area, where fish protein intake was very high. Both cohorts had local physicians who were highly collaborative in the study: Dr. Toshio Onitsuka and Dr. Rokuroh Harada in Tanushimaru, and Dr. Akinori Fukumoto in Ushibuka. The first fieldwork in Tanushimaru was carried out from March 18 to June 19, 1958. This began shortly after Professor Kimura moved to Kurume University School of Medicine and established a new Third Department of

Medicine in January, 1958. All 10 staff members of the new department (listed below) made extraordinary efforts in undertaking simultaneously duties in outpatient clinics, in hospital wards and in student education as well as in the survey fieldwork. They were Professor Noboru Kimura, Drs. Ichiro Furukawa, Hironori Toshima, Shoji Nishimoto, Yoshio Nawata, Shigeru Soejima, Fuminobu Mori, Shigeo Nakakura, Izumi Mori, and Syunichi Kodama. This fieldwork was supported by great contributions of the members of the cardiology laboratory (former chief, Professor Kimura), the First Department of Medicine, Faculty of Medicine, Kyushu University; Drs. Ikuro Goto, Hiroyuki Kimura, Tadashi Irie, Akira Seki, Tsuyoshi Murakami, Eizaburo Yamagata, Yasuhiko Okamura, Hiroto Mashiba, Mikitoshi Hiramatsu, and Toshiro Ohta.

For the first survey, 682 men, aged 40 to 64 years, who were born and had lived in the Chikuyo area of Tanushimaru, were initially registered, while 43 men who had been in foreign countries or in other places of Japan for 10 years or more were excluded because of possible differences in lifestyle. The invitation was therefore sent to 639 men, consisting of 508 men, aged 40-59, and 131 men, aged 60-64. The Japanese cohort thus included men over 60 years in addition to the standard cohorts of the Seven Countries Study, aged 40-59 years. The entry measurements made

Fieldwork in Tanushimaru, 1958

were: *1* age, *2* occupation, *3* eating pattern (24-hour dietary recall) and salt intake estimation (by the amount of soup consumed), *4* area of arable land and amount of physical work, *5* family history, *6* previous illness, *7* drinking and smoking pattern, *8* body size, *9* physical examination, *10* blood pressure, *11* electrocardiogram and exercise stress test by the Master's method[1] *12* serum cholesterol (Keys' method) and serum lipoprotein (Swahn's method), and *13* chest X-ray (indirectly photographed on 35mm film).

The full survey clinic was set up in rooms of the local elementary school. Examinations were carried out in daytime for 441 farmers (69.2%), and in the evening or weekend for office workers and industry employees. Participants who were sick in bed or in hospital received visiting interviewers and examinations. The fieldwork was completed with great collaboration of local doctors. There was, however, one episode in which home visiting staff members were attacked with a shower from a water hose by a participant with a psychiatric problem. The enthusiastic efforts of all staff and paramedical personnel, in addition to the powerful leadership of Professor Kimura, finally enabled the unbelievable response rate in Tanushimaru of 100%!

The fieldwork in Ushibuka started on May 6, 1960, inviting 614 men, aged 40-64 years. Ushibuka is located on the island side of Minamata Bay (later famous for organic mercury poisoning, known as Minamata disease), and the majority of participants were fishermen. Since there was a five-hour drive from Kurume to Ushibuka, fieldwork required two rounds of examination periods; the first round was from May 6 to 14, and the second from June 4 to 12, 1960, with 6 medical and 3-4 paramedical staff residing in a traditional Japanese inn. The very high response rate (99.6%) again largely depended on the great efforts of the staff and devotion of the local doctor, the late Dr. Terunori Fukumoto. The expense of the fieldwork was made possible by relatively low prices and cheap labor in the Japan of that time.

The initial survey was succeeded by systematic follow-up surveys of the cohorts on incidence and death rate for cardiovascular diseases in 1961 (third year), in 1965 (seventh year) and in 1968 (10th year) in Tanushimaru; and in 1963 (third year), in 1965 (fifth year) and 1970 (10th year) in Ushibuka. In the 10-year follow-up examination (1968) the fieldwork was repeated with a larger number of measurements, including: the Rose questionnaire, a pulmonary function test, optic fundi examination, vectorcardiography, serum proteins and fractions, and triglycerides. Among these, optic fundi and serum protein were included to investigate the significance of

[1] The step stress test with double Master's method was included by Professor Kimura. We fortunately experienced no accident with the exercise test in the fieldwork, and this was attributed to a very low frequency of coronary artery disease among Japanese in the 1950s. The exercise step test, single stage, with an intensity approximately 6-7 Mets, may today carry increased risk of accident if performed in a population survey in Japan, due to a growing frequency of coronary artery disease.

Henry Blackburn and Japanese doctors on the boat to Ushibuka, fieldwork 1970.

these as risk factors for cerebrovascular diseases, cerebral hemorrhage, in particular, which was frequent among Japanese in the 1960s. Vectorcardiography was introduced for clinical investigation. This characterized our approach, conducted mainly by clinical cardiologists, in contrast to cohorts directed by public health scientists. The additional measurements later provided the interesting finding of an inverse correlation between stroke incidence and entry serum albumin concentration. Bicycle ergometer stress tests were performed in subgroups of Tanushimaru men in the 1968 examination by Dr. Herman Wolf, with the kind collaboration of Professor Pentti Rautaharju from Canada.

The Period 1977-1992

In March 1977, when Professor Noboru Kimura resigned from Kurume University School of Medicine, he established the Kimura Memorial Heart Foundation, donating to it his retirement fund, and calling for support from medical and pharmaceutical industries. The purpose of the foundation reflected his views, achieved through life-long research and clinical career, that: 'Medical scientists have contributed to progressive advances in therapeutic medicine, although still incomplete. However, the real task of medical scientists must be directed not only to factors acting negatively against health but also to factors positively promoting health as a gatekeeper of healthy life.' In order to achieve this goal, the foundation aims to support preventive medicine for cardio-cerebrovascular diseases and broad educational activities to spread knowledge of primary prevention to the general public.

Dr. Hironori Toshima M.D. succeeded Professor Kimura as principal investigator of the Japanese cohorts in April 1977. Celebrating the founding of the Kimura Memorial Heart Foundation, Professor Toshima started a new survey in Tanushimaru in the spring of 1977. The study was designed to examine time trends in cardiovascular diseases and in their risk factors, since Japanese traditional lifestyle had made remarkable evolutionary changes during the 20 years since the first

survey in 1958. The newly selected cohort consisted of 590 male farmers, aged 40 to 64 years, a cross-sectional sample, including some who participated in the first survey in 1958. Of these, 573 participants completed the examination with a response rate of 90.1%. In 1982, five years later, when a systematic follow-up was conducted, the cohort was extended to women and widened in age range, inviting men and women aged 20 to 69 years. The number of measurements also increased, including HDL-cholesterol, hematocrit, creatinine, GOT, GPT, r-GTP etc. On the other hand, no systematic population survey has been carried out in Ushibuka since 1970, because incidence and death rate there showed no difference from those in Tanushimaru or from statistics derived from other population studies in Japan. Also, the long distance from Kurume required much higher costs. However, yearly follow-up on morbidity and mortality in the initial Ushibuka cohort has been regularly continued by physicians sent from Kurume University Hospital to the Fukumoto Hospital in Ushibuka.

In 1989, 30 years after the first survey, when further changes in Japanese lifestyle and environmental factors had occurred, an additional population survey was designed, inviting *all* inhabitants aged 40 years or more living in the same region in Tanushimaru as the first cohort in 1958. To survey 752 male and 707 female participants, the fieldwork was carried out from June 19 to July 12, 1989, with a response rate of 89% in men and 70% in women. The 1989 survey added measurements of: *1* HbA1c, to assess the frequency of diabetes, *2* serum apoproteins, and *3* 24-hours physical activity recording for estimation of average daily energy expenditure, among a sample of 272 men farmers aged 40 to 69.

Dietary surveys were performed by the 24-hour recall method since the first study in 1958. Chemical analyses were carried out of duplicates of meals, as consumed by randomly selected individual men during a seven-day period in 1964 and a three-day period in 1984.

Since the start of the fieldwork in 1958 more than 100 physicians from the Third Department of Medicine, Kurume University School of Medicine contributed to the surveys, but all their names, unfortunately, cannot be listed. Major staff who conducted these investigations under the leadership of Professors Kimura and Toshima were: Drs. Yuhki Nakayama (1965-1970), Hiromi Tashiro (1970-1985), and Ryuichi Hashimoto (1985 to the present).

Results of the Analyses carried out since 1977

Changes in cardiovascular risk factors in Tanushimaru.

The frequency of obese persons with a Body Mass Index exceeding 26 was 8% in 1958, and gradually increased to 11% in 1977, and to 18% in 1982. This increase con-

tinues in the latest survey and is highest in those aged 40 years and older. The average of the sum of subscapular and triceps skinfold also increased from 15-17 mm in 1958 to 40 mm in 1989, showing remarkable anthropometric changes. The frequency of diastolic hypertension (diastolic pressure ≥ 95 mmHg) gradually increased up to 20% in 1982, in parallel with the increase in obesity. Subsequently, however, a trend downward was observed, in part due to an 8% increase in those under anti-hypertensive medication.

Average serum cholesterol level (Anderson-Keys method) in men of the original cohort, aged 40-64, was 150±41 mg/dl at entry (1958) and remained unchanged during 10 years of follow-up (149±30 mg/dl in 1968). The average cholesterol levels (enzymatic method) in the subsequent new cohorts aged 40-64 increased rapidly to 161±32 mg/dl in 1977, to 178±32 mg/dl in 1982, and to 188±37 mg/dl in 1989. The increase was greatest in the age group 40-44 years. These changes in Body Mass Index, sum of skinfolds, diastolic blood pressure, and serum cholesterol were attributed in part to a decline of physical labor, and widespread use of cars and automated farming machines. The shift away from the traditional Japanese diet could also accelerate these changes.

Changes in dietary pattern in Tanushimaru.

The analysis of data obtained by 24-hour dietary recall showed that total caloric intake was highest, 2,837Kcal/day, in 1958, presumably due to regular strenuous physical labor. The total caloric intake decreased to 2,000-2,200 Kcal in 1968, and then remained level, a finding consistent with the average intake derived from the Japanese national survey. The nutrient pattern also changed considerably. Carbohydrate, in percent of calories, markedly decreased from 78.1% in 1958 to 60.6% in 1989. This decrease contrasted with remarkable increases in protein intake from 10.9% to 15.6% and fat intake from 10% to 21.6%.

Comparison of 10-year mortality and incidence rates of stroke and myocardial infarction in Tanushimaru (1958-1968 and 1977-1987).

The 10-year mortality and incidence rates for stroke and myocardial infarction were compared between cohort 1 (participants in 1958) and cohort 2 (participants in 1977) in Tanushimaru. The age-adjusted death rate from all-causes declined to half, from 15.2/1,000/year in cohort 1 to 7.3/1,000/year in cohort 2. Among these, there was a dramatic reduction of stroke mortality from 3.8/1,000/year in cohort 1 to 0.3/1,000/year in cohort 2. Death rates from infectious diseases including tuberculosis and pneumonia, or those from other causes, also showed a considerable decline from 6.6/1,000/year in cohort 1 to 1.8/1,000/year in cohort 2. On the other hand, death rates from cancer, myocardial infarction or sudden death showed no significant change. In analysis of incidence rates, a 50% reduction of stroke

occurred, while there was no appreciable trend in the incidence of myocardial infarction: 0.6/1,000/year in cohort 1 and 0.9/1,000/year in cohort 2.

Epilogue

As observed in Tanushimaru, there has been a remarkable reduction in stroke deaths (cerebral hemorrhage in particular) in Japan, while mortality from myocardial infarction is still very low. There seems little doubt that these trends in cardiovascular disease mortality have been due to socio-economic development of this country. The deficient food supply before 1960 is now converted to excess. Strenuous physical labor is now replaced by automated farming machines and cars, leading to an increase in the obese population due to lack of physical activity. Nevertheless, Japanese currently enjoy the greatest longevity in the world, with only a minimal increase, so far, in coronary heart disease deaths. The lessons from the Seven Countries Study suggest that this longevity may be attributed to the traditional eating pattern of Japanese, which depends on rice as the major source of energy and effectively limits the fat intake at 25%. We conclude from the Seven Countries Study that the current Japanese diet may be optimal to prevent coronary artery disease and stroke, but careful surveillance is needed due to the increasing intake of saturated fatty acids.

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13

DIETARY SURVEYS IN THE SEVEN COUNTRIES STUDY

F. Fidanza and D. Kromhout

From the beginning of the Seven Countries research program, diet was thought to be an important determinant of coronary heart disease. Already in the 1950s it was suggested that differences in dietary fat could explain differences in mortality from coronary heart disease, with serum cholesterol as an intermediate. Dietary intervention studies showed that manipulation of the amount and kind of fat influenced predictably the cholesterol concentration in the blood. It was therefore decided that the collection of dietary data should be a part of the Seven Countries Study. In total, 12,763 middle-aged men were enrolled in the study. With the laborious dietary survey method commonly used at that time, the seven-day record method, it was impossible to survey all men. Therefore, subsamples were selected for detailed dietary surveys.

Dietary Survey Methods (F. Fidanza)

When I was in Minnesota in 1953, Sadye F. Andelson (USDA-Washington) was carrying out a dietary survey on Minnesota business and professional men participating in a long-term study of aging conducted by the Laboratory of Physiological Hygiene of the University of Minnesota. The record-by-weight, or food record method, was used for two consecutive weeks. It was a useful experience to spend time with her and the five nutritionists or home economists involved in that study. The same forms, with minor modifications, were then used in dietary surveys in Naples.

In Finland, the weighing method for dietary surveys was in common use, including the 1956-57 studies on food consumption of rural families in East and West Finland. I participated in the diet-serum cholesterol studies in Finland and had the opportunity to visit Paavo Roine and Maija Pekkarinen at the old building of the Department of Nutritional Chemistry of the University of Helsinki, Viiki, Helsinki. They explained in great detail the methods they used, later sending me the forms translated into English.

I quote a paragraph from an unpublished document by Paavo Roine: 'The dietary surveys in Finland, Greece, Italy, and Yugoslavia were carried out by the weighing method, since it was considered in the prevailing conditions to give the most accurate and reliable data on the quality and quantity of the food consumed, and particularly on the consumption of the individual men surveyed. Since the weighing was done by outside investigators, the families could be chosen by random sampling. Accurate information was thus also obtained on the food consumption of such families and/or individuals who would not have been able to estimate reliably or to keep records or their own food consumption. It is also to be noted that the weighing method provides data on the amount of food actually eaten by the people because all the inedible material, the table waste and the left-over food are carefully weighed.' In the Seven Countries Study, after considering the limitations of this method and providing details on the procedure, chemical analysis on a subsample of food composites was recommended to check results obtained by calculation, and especially to determine the intake of fatty acids.

In the three areas of Italy we used this method and procedure. The survey was carried out by nurses of the Italian Ministry of Health (Maria Giulivi Pessoli, Alba Donnini, Dianora Mengoni, Emma Montevecchi, and Maria Organo). They were trained in nutrition and dietary surveys and involved in a pilot study in Montegiorgio in November 1959. The survey was carried out in three different seasons of the year 1960, and in January 1961, on 99 families.

The nurses did a wonderful job and left an excellent impression on the surveyed families, which was very helpful for future work. In Nicotera, in the south, the selected group of 30 subjects was reduced to 24 because one nurse fell sick. Then, seven subjects refused to cooperate with the second season survey and were substituted by 13 new subjects with similar characteristics. The final result was that 17 subjects were examined in all three season surveys. The analysis of variance showed no statistical difference between the 17 and 7 subjects in the first survey. Even a subsample of 1% can be representative if the population has relatively homogeneous habits. The computation of dietary data of 1,251 subjects for seven days would take too much time, considering the simple, slow and 'noisy' calculators available at that time.

For the subsample of Rome railroad men, the seven-day food diary method was used in June-July 1969 because we had gained experience with this method and it was more practical for that particular group of subjects.

In Crete the dietary survey was carried out by Helen Sdrin (teacher at the School of Home Economics in Athens) and her staff. I was involved in the preparation of food composite samples in the headquarters in the kitchen of Herakleion Hospital. The cook, George Arniotakis, was very helpful in grinding the food composite with a large vegetable grinder, the food having arrived the evening before in covered

Preparation of aliquots of foods at the market of Zrenjanin, 1963.

enamel jars. Because some subjects consumed pomegranates, it was a problem to grind the seeds, solved by pounding the seeds in a mortar. During this work, the subjects, mostly farmers, speaking Venetian-Italian fluently, told me that their breakfast early in the morning was a glass of olive oil! George was formerly a cook for King Farouk; we became friends and at the end of the work he cooked an excellent 'stiffado' (ragout of beef with big onions cooked for several hours) for us.

I was also involved in Yugoslavia in preparation and analysis of food composites. Ratko Buzina's associates, Branka Tiefenbach (called Seka) and Agneza Horvat from the Institute of Public Health of Zagreb, were helpful; Seka had worked with me in Naples for a time so that comparable results were obtained.

In order to plan the presentation of results on dietary surveys at the Sixth International Congress of Nutrition in Edinburgh on August 1963, I organized a meeting in Milan from February 10 to 13, 1963. In the provisional program for the Congress I suggested the following speakers: Paavo Roine (methods of dietary surveys in Finland, Greece, Italy, and Yugoslavia), Maija Pekkarinen (results of dietary surveys in Finland), Demetrios Galanos (results of dietary surveys in Greece), myself (results of dietary surveys in Italy), Ratko Buzina (results of dietary surveys in Yugoslavia), and Cornelis (Kees) den Hartog (methods and results of dietary surveys in the Netherlands). At the meeting, held at the Board Room of the Laboratorio Biologico Zanoni, Kees den Hartog, Paavo Roine, and myself were present for a fruitful discussion and a pleasant time. We decided to present the available results

on dietary surveys in a session of the International Congress of Nutrition in Edinburgh and to publish all papers in the Netherlands Journal of Nutrition, 'Voeding'. In addition, Den Hartog suggested collecting all these papers in a booklet, now the famous so-called 'Red Book': Dietary Surveys and Epidemiology of Heart Disease (1). This book became a standard research reference in nutritional epidemiology. The most rewarding result of the Milan meeting was my good friendship with Kees den Hartog that lasted until he died recently.

The week before the International Congress of Nutrition in Edinburgh, John Durnin organized, in Glasgow, a Workshop on Dietary Surveys Methodology. I presented a paper on 'Diet Methodology-Epidemiological Aspects', considering the advantages and disadvantages of the methods used. Theodora van Schaik illustrated the dietary history method also used in Zutphen (The Netherlands) in 1960. During free time at the Glasgow University Guest House she defended the dietary history method and I defended the weighing method. I have not changed my position, but in the first follow-up in 1965 of the two rural Italian cohorts (Crevalcore and Montegiorgio) we also used the dietary history method on the 1,536 subjects examined. Retrospectively this was a fortunate decision, because we found no difference between the two methods in regard to mean population food and nutrient intake. Moreover, with the dietary history method, a wider scope of dietary data is possible. Accordingly, in the subsequent follow-ups of the Italian rural cohorts, both methods were used.

Processing and Chemical Analysis of Cross-cultural Food Intake Data (D. Kromhout)

Fourteen of the sixteen dietary surveys in subsamples of the Seven Countries cohorts took place between 1959 and 1964. Two surveys, Rome Railroad and Ushibuka (Japan), were held later, around 1970. The seven-day food record was used in 14 of the 16 cohorts, while one-day records were used in the U.S. Railroad and four-day records in Ushibuka. Participants recorded what they ate and drank during the period and the amounts consumed were weighed as well. In 13 of the 16 surveys, foods were recorded as the edible part of the raw products and, in 3 of the 16, as prepared products. To compare the different cohorts, all quantities of the prepared products were converted into quantities of raw products in a standardized way. This was done by one dietitian in 1985 and 1986, Annemarie Jansen from the Netherlands, in close collaboration with investigators from the different countries.

All foods consumed by men in the different cohorts were classified in 15 homogeneous food groups. The 16th group was heterogeneous. The average consumption of these 16 food groups was calculated, per person, per day, for each cohort, and the results published (2). Characteristic differences in food consumption pat-

terns in the different countries had been observed in the 1960s. In Finland, the intake of milk, potatoes, edible fats, and sugar products was very high. A similar but lower intake pattern was observed in the Netherlands. Fruit, meat, and pastry consumption was high in the United States; cereal and alcohol consumption were high in Italy; and bread consumption was high in Croatia and Serbia, except for those in Belgrade. In Greece, the intake of olive oil and fruit was high while the Japanese cohorts were characterized by a high consumption of fish, rice, and soy products.

Food tables with detailed information on the fatty acid composition of foods in the seven countries were lacking in the 1960s. Therefore the fatty acid composition of food composites was determined for 13 of the 16 cohorts. These analyses were carried out by Dr. Joseph T. Anderson at the Laboratory of Physiological Hygiene, University of Minnesota and Flaminio Fidanza at the Human Physiology Institute, University of Naples (Italy). The results showed a sevenfold difference in saturated fatty acid intake between eastern Finland and Japan (3). Later, however, the interest of the investigators became broader than for fatty acids. Therefore, it was decided in 1987 to attempt to construct, retrospectively, composites representing the average food intake of the 16 cohorts *during the baseline survey*. These equivalent composites were purchased from local markets by two Dutch dietitians, Annemarie Jansen and Ester Goddijn, in close collaboration with the local investigators. The foods were transported in coolers to the laboratory of the Department of Human Nutrition, Agricultural University, Wageningen, the Netherlands (Martijn B. Katan, Ph.D.). There the foods were cleaned and equivalent composites prepared according to the average consumption patterns of the cohorts. The foods were homogenized and frozen at -20°C until chemical analysis of the different nutrients took place. The chemical analyses were carried out in 1987 and 1988, the macronutrients and minerals determined at the Department of Human Nutrition; the vitamins and trace elements and non-nutritive substances at the Department of Micronutrients and Natural Toxins, DLO, State Institute for Quality Control of Agricultural Products,

Unpacking of foods sent to the central laboratory in Wageningen, The Netherlands, 1987

Wageningen, (Ir. Peter C.H. Hollman), and trace elements at the Laboratory of Analytical Residue Research, National Institute of Public Health and Environmental Protection, Bilthoven (Huub Vaessen Ph.D.). These data will be used to analyze, at the population or cohort level, relations between habitual nutrient intake at baseline and 25-year mortality rates from chronic diseases.

Individual Dietary Data in Netherlands, Italy, and Finland

All men in Zutphen (Netherlands) were surveyed with the dietary history method in 1960, 1965, and 1970. This method was also used in Crevalcore and Montegiorgio (Italy) in 1965 and again in Crevalcore in 1970. In 1969 Finnish colleagues also decided to use the dietary history in the third round of the East-West Study. Therefore a unique data set could be constructed with dietary information collected with the same method in about 3000 men in three different cultures. It took about 20 years, however, before these data became available for analysis, due to the development of modern computers.

In 1987 Daan Kromhout, Alessandro Menotti, Leena Räsänen, and Maija Pekkarinen decided to code these data in a uniform way. Food groups were composed and computerized food tables, containing the foods used in the 1960s and their nutrient content, were prepared for the three countries. A data base is currently available containing 33 food groups and 24 nutrients. This will be used to study diet - disease relations on the individual level in these five cohorts. The dietary data collected between 1960 and 1970 can then be related to mortality from different diseases during 15-25 years of follow-up. The great advantage of this data base is the large variation in dietary patterns, among which it will be easier to find associations between dietary variables and disease outcomes than among homogeneous populations within a country.

Because of the availability of individual dietary data collected in the period 1960-1970, it was decided to gather information with the same methodology in the 30-year follow-up surveys. This will make it possible to study changes in dietary patterns in the aging cohort in different European cultures. In 1989, for example, a random sample was surveyed of 227 of the 524 men who were still alive in Finland. In 1990, 560 men were surveyed in the Netherlands and in 1991, 421 men in Italy. These data will be used to describe differences and changes in dietary patterns and nutrient intake in men aged 70-90, and to examine cross-sectional associations between diet and health. Later, these data will be used to study associations prospectively at the individual and population level.

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14

MAJOR RESULTS OF THE SEVEN COUNTRIES STUDY

H. Blackburn and A. Menotti

Demonstration of Feasibility

Prior to the Seven Countries Study (SCS) no one had attempted to compare cardiovascular disease (CVD) frequency and risk between defined populations in a systematic manner. The SCS demonstrated that with goodwill, planning, and hard work, leadership and collaboration could be found, funding obtained, and research carried out, despite many difficulties.

Population Differences: Cross-sectional

The SCS was the first to establish credible data on CVD prevalence rates in contrasting populations, with differences found on the order of five to 10 fold in coronary heart disease (CHD). The SCS was the first to document population differences in the means and distributions of serum cholesterol, with the dramatic example of the almost non-overlapping values between men of the same age in Japan and eastern Finland of the 1960s. The SCS demonstrated remarkable differences in composition of diet in otherwise similar rural, stable, agricultural-pastoral populations: between 3 and 22% for saturated fatty acid calories daily and 9 to 40% total fat calories.

Detailed, deciled distributions were reported for the first time of skinfolds; height, weight and relative body weight; systolic and diastolic blood pressure, and serum cholesterol for all areas of all seven countries.

The concentration of blood serum cholesterol at entry showed greater differences among the 16 cohorts than any other risk factor. The mean ranged from 160 mg/dl or less in Serbia and Japan, to 260 mg/dl in Finland. There was a low order individual correlation of serum cholesterol with age, blood pressure, and body mass index.

Entry surveys found lack of individual correlation between electrocardiologic findings of left axis deviation and major risk characteristics, and strong correlations between: high amplitude R waves on ECG and systolic blood pressure; negative T-waves and systolic blood pressure; post exercise ST depression and sum of skin-

folds and systolic blood pressure. There were negative associations of exercise ST changes and cigarette smoking; strong positive associations of left ventricular hypertrophy and heavy work; and strong relationships of infarct Q waves to serum cholesterol and systolic blood pressure.

Population Differences: Follow-up

The SCS was the first to establish credible data on CVD incidence rates in contrasting populations, with differences on the order of six to eightfold in CHD. The 5-year follow-up found favorable all-cause death rates in Greece, Japan, and Italy compared with the other areas, as well as a lower incidence rate of coronary disease and new electrocardiographic findings in those areas.

A remarkable excess was found of 5-year deaths among those with an old infarction, in the order of 10- to 20-fold.

Ecologic correlation was weak between CHD incidence and the proportion of the population sedentary, overweight, or obese, or with elevated systolic pressure >160 mmHg. Diastolic pressure >95 showed, however, a strong relationship with CHD. The strongest consistent relationship was between the population prevalence of entry serum cholesterol values greater than 250 mg/dl and CHD incidence. There was also a strong correlation of CHD incidence with saturated fatty acid intake at entry.

Low CHD rates in a cohort were not compensated by an excess of other death causes. Total, all-causes death rate reflected well the death rates from CHD.

There was an indication overall of the importance of blood pressure and serum cholesterol in individual prediction of 'hard criteria' of coronary death and infarction, a lack of significance of body weight, significance of smoking habits in U.S. but not in European cohorts, and weak relationships of CHD with physical activity.

In the 10-year follow-up experience, among the 12,000-man cohort free of CVD at entry, the 10-year total death rate was less than 75/10,000 in Crete, Japan, and Croatia and was 250 or greater for Finland, U.S. Railroad, Zutphen, and Serbia.

Correlation of CHD death rates in Seven Countries cohorts with WHO vital statistics on coronary deaths was 0.98; for all-causes death rates the correlation was 0.86, indicating that SCS cohort data have generalizability to regional and national experience.

A higher death rate from neoplasms in northern Europeans was due to a threefold excess of lung cancer.

It was found that age standardization *by single years of age* is required in analysis, due to the strong influence of age on incidence of CHD. For example, the difference of one year of age in 10-year CHD incidence was 5 to 6%.

The individual correlation of age with major risk factors was trivial, but age was

the strongest risk predictor for CHD incidence and death from all-causes. However, despite the great difference in CHD rates, the force of age itself, in regard to the incidence of hard CHD, was similar between northern and southern Europe.

In all areas, men in the top 20% of the age-specific distribution of blood pressure at entry had twice the incidence of CHD, and this was similar for all areas.

All-causes death rates were only slightly correlated with average serum cholesterol level, while there was a highly significant correlation of cholesterol level with 10-year CHD deaths and a negative correlation with all causes of death other than CHD combined. Thus, the SCS was one of the first studies to demonstrate the inverse relationship between serum cholesterol level and non-cardiovascular disease risk.

Serum cholesterol concentration was a particularly important individual risk factor for CHD at levels greater than 220 mg/dl, while at less than 200 mg/dl, decreasing cholesterol concentrations tended to be associated with increasing rates of non-coronary death.

Strong prognostic power was found of the ECG, particularly for ischemic and junctional type ST depression after exercise, for negative T waves independent of ST depression, and for post-exercise arrhythmias. The prognostic importance was shown of major Q and QS waves, and of negative T waves and atrial fibrillation.

A remarkable finding was that in Italy, Greece, and Japan cigarette smoking was a minor risk factor for all-causes and CHD deaths, in part due to few CHD events. In the other cohorts there was a strong individual relationship of smoking to coronary and non-coronary causes of death, and the risk of cancer rose linearly with cigarette smoking dose.

Weight and Physical Activity

Cohort differences in 10-year CHD death rates were not significantly related to average relative weight or obesity. Within none of the areas was relative overweight or obesity associated with excess risk of all-causes death. In fact, total deaths were *inversely* related to relative body weight and obesity in Finland, Croatia, Italy, Greece, Serbia, and Japan. Ten-year incidence of coronary heart disease was not significantly related to body mass, and the probability of death (all cause) in 10 years was least for men with greater than average relative weight or fatness.

Distributions of physical activity of occupation did not explain cohort differences in the incidence of CHD. Where physical activity was important in predicting individual risk of coronary disease or early death, it seemed to be due to interrelations with other risk factors. However, few of the occupations represented in the SCS involved heavy, anaerobic work.

Other Characteristics

Resting heart rate was significantly lower in men active physically, and 10-year death rate was linearly related to the entry pulse rate.

An increase of one year in age was associated with an average decrease of 1% in vital capacity and 1.4% decrease in 3/4 second FEV. Timed vital capacity was significantly and inversely related to all-causes deaths, though CHD was unrelated to entry vital capacity. Timed vital capacity was more prognostic than total vital capacity.

For diet, within-individual variation in the same cohort was of the same order as between-individual variation. This provided another demonstration of statistical theory: under such conditions, individual serum cholesterol and nutrient composition of diet cannot be found correlated without repeated surveys to reduce the effects of intra-individual variation.

Multivariate Analyses

Partial correlation analysis, including dietary saturated fatty acid content, found no significant correlation between dietary sucrose and CHD incidence. Cohort comparisons showed the strongest correlation of milk and cheese with CHD incidence.

Only two entry risk variables were significantly related to differences in CHD incidence among cohorts: blood pressure and blood cholesterol, accounting for 40 and 42% of the variance in CHD death rate. Together, they accounted for about two-thirds of the variance.

The risk of 10-year deaths from all-causes was least for men above average in relative body weight and skinfolds in multivariate analysis, including other major risk factors.

In multivariate analysis, habitual physical activity and resting heart rate at entry were significant predictors of all-causes death and coronary death in Europe.

Systolic and diastolic blood pressure were highly significant risk factors for death and CHD incidence in multiple logistic analyses, but neither was superior.

Multivariate discriminatory power of risk factors for CHD death was far superior to their prediction of all-causes death.

Multivariate solutions from experience in one area gave generally good prediction of relative CHD risk in other areas but gross errors in prediction of absolute risk. The 'southern solution', for example, greatly underestimated the absolute risk of coronary deaths in northern European cohorts. These multivariate analyses across cultures lead to two possible conclusions: 1) at entry, measurements were not representative of long-term characteristics of men in the different areas, or 2) unidentified variables, unrelated to those considered in the SCS, contributed to the increased risk of Americans and northern Europeans, or alternatively, were 'protective' in southern Europeans and the Japanese.

In all European areas there was a significant rise in mean serum cholesterol in the first 10 years of the SCS. This trend upward in cholesterol was more marked in southern than in northern Europe, more marked in the younger men than in the older and was presumably based on dietary changes on-going in Europe.

The specter that a low incidence of CHD necessarily involves a trade-off with other, less acceptable causes of death, was laid to rest. The SCS gave clear demonstration of the contrary that CHD deaths are generally unrelated to death rates from other causes in these relatively developed countries. The conclusion is that effective prevention of CVD does not necessarily lead to enhancement of other causes of death, but rather, can result in lower age-specific death rates overall!

Design and Method Innovations

The SCS was probably the first, and certainly the first in cardiovascular disease (CVD) epidemiology, to carry out cross-sectional surveys of populations contrasting in diet, in samples adequate to demonstrate differences in prevalence and early-year incidence, as well as to combine this with cohort follow-up for incidence and mortality, for up to 30 years in many areas.

The SCS demonstrated the validity of dietary survey methods to characterize the diets of whole populations, and made important contributions to the measurement of individual and population diets.

The SCS made basic contributions, as well, to the methodology of population studies with respect to electrocardiographic classification, clinical procedures, risk factor measurement, blood lipid analyses, and skinfold measurement.

In addition, contributions were made to sampling for epidemiological surveys. Less than perfect response rates do not necessarily mean biased samples in regard to physical characteristics. Moreover, complete responses in rural villages may represent the generality of rural men of an entire country.

Many contributions were made, as well, to the practicalities of fieldwork, including the number of people per day examined, number of days or number of weeks in the field, timing of the fieldwork in regard to local conditions, establishing a roster, engaging local assistants, transportation, and training and organization of the field team.

Methodological deficiencies were found of occupational classifications in respect to physical activity.

Population Correlations

The SCS was the first to compute population (ecologic) correlations between risk factors and disease incidence, demonstrating significant population correlations as

well as thresholds for atherosclerotic diseases and establishing the precision with which CHD death rates can be predicted by knowledge of the average serum cholesterol level of a population, and the increasing precision of that prediction over a 15-year follow-up.

It also demonstrated the remarkable departure from the prediction line for particular populations such as East Finland, where CHD rates were greater than predicted by the mean serum cholesterol values and the island of Crete, where the rates were less than predicted by those values, opening important new questions about causation.

The Force of Risk Factors

The SCS was the first CVD study to apply partial correlation coefficients derived from relationships between risk and disease incidence found in one country or group of countries to those in another. This showed the universality of risk factors as predictors of individual relative CHD risk in widely contrasting cultures. But the SCS was also the first to demonstrate the different force of a risk factor in populations and in individuals, finding the slope of the individual risk factor-CHD relationship approximately twice as great in the United States as in Europe, and in northern as in southern Europe.

Risk Factor Changes

The SCS was among the first to demonstrate dramatic changes in a decade in both directions (in means and distributions of risk characteristics in whole populations), confirming the overwhelming role of culture and environment in determining differences and changes in chronic disease risk, particularly cardiovascular diseases.

The SCS was among the first to demonstrate the predictive importance of change in risk characteristics, suggesting the particular importance of population change in cholesterol and blood pressure levels in the risk of cardiovascular diseases.

Long-term Prediction

The SCS was one of the first to examine, in prolonged cohort follow-up study, the relationship between baseline risk characteristics during health and subsequent longevity, variously defined as survival for 25 years, or to age 75, or 85. It showed the importance of cigarette smoking in long-term survival, the lesser contribution of blood pressure, and the very little contribution of serum cholesterol and body mass index.

The SCS was one of the first to illustrate the variety and complexity of the relationship between body weight, body mass and obesity, and disease rates, including total mortality and survival. The shape was highly different between cultures, from absolutely flat relationships, for example, of weight measures with CHD, to U-shaped or inverted U-shaped, to monotonic linear positive relationships, and in occasional cases, even inverse relationships. The more recent findings of Keys suggest that in some cultures longevity and survival are actually greater in those who gain weight in middle age than in those who do not gain, or who lose weight.

Fifteen-year mortality follow-up confirmed the experience of the 10-year follow-up in all regards: risk functions of northern Europe and the U.S. overestimated the coronary mortality of southern Europe, and half of the area differences in CHD death rate were explained by average blood total cholesterol level alone, with little added contribution from the other major risk factors.

Population (ecologic) correlations among the 16 cohorts of the ratio of mono-unsaturated to saturated fatty acids were inversely related to CHD, cancer, and all-cause mortality.

Twenty-year follow-up mortality revealed that 81% of the difference among cohorts in CHD deaths could be explained by mean saturated fatty acid intake.

Individual correlations revealed that age and blood pressure were the only consistent universal predictors of individual risk of CHD and all-causes death. An inverse correlation was found between blood cholesterol levels and stroke mortality.

The time integral of the changing level of risk factors during the first three surveys, largely independent of the initial level, enhanced prediction of subsequent mortality.

Twenty-five year follow-up revealed a reduced predictive power of entry cholesterol level for long-term CHD mortality. This long-term follow-up found reordering among the cohorts' ranking of coronary mortality rates, with Zrenjanin (Vojvodina) eventually achieving the highest rates. Absolute and relative increase in coronary mortality was greatest in Zrenjanin and Velika Krsna (Serbia), accompanied by very large increases in average cholesterol levels, especially in Zrenjanin, far greater than in other southern European cohorts. This contrasted to no change, or to decreased cholesterol levels, in northern Europe and the U.S.

Public Health Implications

Frederick Epstein has, in this volume, summarized elegantly the public health implications of these SCS results. It is fitting that this be done by a person outside the investigators group, yet a person having a longstanding professional interest and a supportive role in Seven Countries undertakings.

Clearly, a major result of the SCS has been the concept of *population* causes and phenomena involved in mass diseases such as CHD, hypertension, and stroke. We have come to appreciate that we are dealing with *mass* cultural phenomena that influence already widespread individual susceptibility and lead to the heavy population rates of disease. This concept has played the central role in development of the population strategy of prevention, complementing the individual medical strategy. It has stimulated the research on population causes and on community-wide preventive strategies which characterizes the on-going work of Seven Countries investigators.

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15

PUBLIC HEALTH IMPLICATIONS OF THE SEVEN COUNTRIES STUDY

F.H. Epstein

Ancel Keys never wrote or talked much about public health as such but rather contributed to its mission and success. However, it is interesting and important that 'public health' is part of the title of a historical paper, based on a lecture presented in 1953, in which he presented, for the first time, his views on the relationship between cholesterol and the diseases due to atherosclerosis (1). In the introduction, he points out that the frequently narrow concept of public health should be extended to wider horizons, 'to prevent or decrease the incidence of *all* forms of illness and disability, not merely those that are infective or occupational in origin'. Keys states that major public health attention is required when there are large numbers of the population suffering disability and death from diseases for which private medical practice is making little headway, and when there is hope that measures applicable to the general population can be found to alter the incidence of these diseases; he adds that coronary heart disease fulfills these conditions. It is clear, therefore, that Keys had the public health implications of his work in mind from the very beginning. The Seven Countries Study is, as Keys states in his own contribution to this book, the culmination of work which began in Minnesota in 1947. But it took some 10 years for the major project to get under way after completion of the many exploratory investigations in the intervening years.

The definition of public health is not as evident as it might seem. One proposal is that it '... consists of all the things we as a society do collectively to assure the conditions in which people can be healthy' (2). This definition has the sanction of a special committee of the Institute of Medicine of the National Academy of Sciences of the U.S.A.; it is appealing in being broad, broad-minded, and functional. It will serve the present purpose very well. Under this definition, it is unnecessary to debate to what extent research into the causes of disease falls within the domain of public health, or whether the application of the results of this research is entirely within its realm. All that matters is how the targets can be reached most effectively and efficiently! Along this road there is a continuum from observational studies, like the Seven Countries Study, to testing the results for causality between predis-

posing factors and disease risk by means of intervention studies, and applying the knowledge and understanding gained toward prevention. The Seven Countries Study stands at the beginning of this chain but has had a decisive influence all the way along its course. The present assessment is concerned with the final link, trying to evaluate the impact of the study at the public health level.

Before proceeding further, it goes without saying that no study is an island, like 'no man is an island'. The role of each study must be viewed within the context of the contributions of all the investigations which, over the years, have helped to build up the available knowledge on, in this case, cardiovascular disease epidemiology. An attempt has been made to summarize the saga of this success story (3). In the case of the Seven Countries Study the task is somewhat simplified by the fact that, among the studies which permit international comparisons, it really has no equal. In part, it is an ecological study which makes it possible to relate disease incidence, not just mortality from national statistics, to risk factors and lifestyles, measured by comparable methods; this ecological component has a partial counterpart in the MONICA Project. There is no counterpart to the prospective component because, in no other study, have incidence as related to lifestyles and risk factors been measured according to the same study protocol by the same, standardized methods. There are many separate prospective investigations of coronary heart disease in a number of countries which attest to the universal validity of the risk factor concept in regard to cholesterol, blood pressure, and smoking, but the incidence data are not comparable as the diagnostic criteria are not the same. Another unique feature of the Seven Countries Study is that it combines the advantages of ecological and cohort studies, while largely avoiding the pitfalls of the 'ecological fallacy' since data based on individuals are available at the same time.

No finding from the Seven Countries Study had a greater impact than the sequence leading from dietary habits, especially in terms of dietary fats, to the lipid content of blood, in particular cholesterol, and from there to coronary heart disease risk. In most epidemiological investigations, data on diet are lacking and, if available, are limited in their usefulness for characterizing individuals, on account of measurement error and variability. In the Seven Countries Study, ecological dietary comparisons of groups are supplemented by the dietary investigations of individuals under controlled conditions, carried out independently by the Laboratory of Physiological Hygiene. Drawing on all sources of data, the study has provided the strongest existing evidence that the risk of coronary heart disease is linked to the consumption of saturated fat, and that this relationship is mediated by serum cholesterol. This, of course, is the basis for the current conviction that reduction of saturated fat intake will lead to a reduction of coronary heart disease risk. Firm support comes from preventive trials, but these are confined to high-risk groups and mostly use drugs rather than dietary modification for lowering serum cholesterol. The

results from the Seven Countries Study permit, more than any other data singly or collectively, important though they are, the extrapolation from high-risk groups to the population at large. They are a cornerstone, therefore, of the population strategy of prevention related to diet and serum lipids.

Beyond serum cholesterol and its determinants, the Seven Countries Study has contributed important cross-cultural data on blood pressure which is related to disease risk in all the areas. The same does not apply to smoking or physical activity. This does not in any way suggest that they are not important, but indicates that the constellations of risk factors which add up to total coronary heart disease risk may not be exactly the same in different parts of the world. Furthermore, evidence from other studies must be taken into account, as well as the statistical power inherent in different studies. No single study can answer all questions, but there are few if any studies which have contributed at the same time to as many answers, definite or tentative, as the Seven Countries Study. In the present context, from the all-important point of view of coronary heart disease prevention, the outstanding finding is the demonstration that countries can be graded along a scale of disease risk, and that this risk is related to a series of lifestyles and risk factors. Without the Seven Countries Study, this knowledge would have to be pieced together from a variety of sources which often lack comparability or reliability. These studies also give each participating country a measure of its own risk status and the factors which influence it. From this, high-risk countries can draw the lesson how to become a low-risk country and low-risk countries can learn how to become or not to become a high-risk country. Examples of the former are the U.S.A., Finland, and the Netherlands that showed large decreases in CHD mortality during the last two decades. An example of a low-risk population that became a high-risk population is the Serbian cohort Zrenjanin (Vojvodina). The latter lesson is of prime importance to the developing part of the world. It would be very unfortunate if the Seven Countries Study were viewed only within its own confines, without realizing that its findings can be extrapolated to countries resembling those which are included in it. This is one of its great strengths!

The bearing of the study on the population strategy of prevention has already been pointed out. For optimal prevention on the community level, the high-risk strategy must supplement it. While practicing physicians must be involved in both strategies, their immediate role is the protection of people at high risk. Ancel Keys had striking success in enlisting the collaboration of clinicians, many of them leaders in their own countries, both in the Seven Countries Study and, importantly, in the field studies which preceded it in the late 1940s and in the 1950s. Through them, the seeds of thinking in terms of epidemiology and prevention, and of becoming engaged in these fields, were planted in a good many countries, both within and outside the Seven Countries Study. It would be impossible to gauge the influence of

these physicians and their publications, separately and with the Minnesota team, but, empirically, the 'spirit of prevention' seems to be, on the average, more alive in their countries. A certain international halo-effect of these activities also appears to be evident. Perhaps one of the messages of the Study is that medical people support epidemiology and prevention more strongly if they get themselves involved in their pursuit. One of the obstacles to public health action in coronary heart disease prevention is the frequently passive or negative attitude of the medical profession. Practicing physicians are essential 'agents of change' in promoting prevention and the Seven Countries Study has had an impact on these developments.

The influence of the Seven Countries Study, along with the total effort of the Laboratory of Physiological Hygiene, on research into the causes and prevention of atherosclerosis and its consequences is immense. In his introduction to the first Ancel Keys Lecture, Blackburn has tersely and impressively addressed this point (4). It is not only a matter of the huge amount of work done but having opened, in many ways, a new world which stimulated an immeasurable amount of work carried out by others. To this must be added the leadership which Ancel Keys and his senior associates assumed nationally and internationally to further epidemiological research, and to apply the results in the cause of prevention. There is no doubt that all of this dedicated and successful effort played a major role in initiating and intensifying epidemiological research, including the big intervention studies, and the development of national programs for the prevention and control of cardiovascular diseases, both in the United States and some other countries.

How does research lead to action on the public health level? Cardiovascular disease, being a health burden of epidemic proportions, demands preventive action encompassing the whole population. The required action needs collaboration of all people in the population, whether or not at elevated risk, the physicians in the community, the health agencies from the local to the national level, professional societies, the media, research workers and organizations, and policy makers. This chapter is concerned with the public health implications of the Seven Countries Study. Has it influenced preventive action on all of these levels? Most likely it has, but it would be hard to arrange the targets in order of the impact which the Study had on them. Does it matter? Can we do more than give our best in doing good research and see to it that those in a position to turn it into action are aware of the scientific evidence and its implications? In the Seven Countries Study, all of this has been done!

The Seven Countries Study has not only provided crucial evidence for the potential of coronary heart disease prevention; it has also created a new model and approach for studying geographical differences in the frequency of non-communicable diseases and searching for their causes. In his review of Ancel Keys's book on the Seven Countries Study, Stallones writes: 'Keys's contributions to the epidemi-

ology of coronary heart disease are enormous, but this report suggests that what he has begun may be far greater even than what he has done.' (5) The public health implications of this monumental work, therefore, will in all probability, extend to horizons which cannot yet be seen.

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THE FUTURE OF THE SEVEN COUNTRIES STUDY

D. Kromhout, A. Menotti and A. Nissinen

It is almost 40 years since the first ideas for an international collaborative study on the epidemiology of cardiovascular diseases were developed. In 1958 the fieldwork was started in Dalmatia. In almost all cohorts, three rounds of fieldwork were carried out every fifth year. After the third round, mortality follow-up was continued in all 16 cohorts. The 25-year mortality follow-up of all cohorts was terminated in 1989. The data on 12,763 men, originally 40-59 years of age, were collected between 1958 and 1989 and are now available for analyses. In Finland, Italy, and the Netherlands additional surveys were carried out after 25 and 30 years of follow-up, and a 35-year follow-up is being planned for these three countries. After 25 years of follow-up, the men were 65-84 years old and therefore the study was extended into a broad gerontological survey. Fortunately, 25-year follow-up surveys were carried out in the three Serbian cohorts of the Seven Countries Study, and it is hoped that studies on these cohorts can be realized in the future.

The aims of the original Seven Countries Study were described by Ancel Keys on page 315 of the 1980 monograph: 'to compare the incidence of coronary heart disease in diverse populations, to find and evaluate relationships between the incidence of the disease and the characteristics of men before clinical disease was evident, and to examine the universality, or variability, of these relationships in contrasting populations.' On page 162 of the 1970 monograph he stated that 'from the inception of the research program, an important focus was on the diet and its possible relationship to the etiology of coronary heart disease.'

The major results of the Seven Countries Study have been described in Chapter 14 and the public health implications in Chapter 15. However, in most of the analyses carried out, only baseline data of the 16 cohorts have been related to 10 or 15 years' mortality experience. The data of the re-examinations collected in the second and third round have not been fully explored. Therefore, much is still to be learned from the data collected during 25 years of follow-up, including these examples of current or planned analyses.

Menotti and co-workers have already shown that, besides the entry level of

blood pressure, *changes* in blood pressure are independent individual predictors of CVD risk. Similar analyses will be carried out for changes in body weight and serum cholesterol. Currently, there is a great interest in the relation between serum cholesterol level and non-cardiovascular diseases. The Seven Countries Study data provide the possibility to study these associations in different cultures and throw light on this complicated issue. In all cohorts information on lung function was collected at least once. This information will be used to study associations between lung function, mortality from chronic diseases, and all-causes deaths.

Individual dietary data were collected in Zutphen (The Netherlands) in 1960, 1965, and 1970, in Crevalcore (Italy) in 1965 and 1970, in Montegiorgio (Italy) in 1965, and in East and West Finland in 1969. The dietary survey method used in all these cohorts was the dietary history. Therefore a unique data set is available of about 3,800 men, aged 40-69, at baseline who were followed during 15-25 years in relation to mortality experience. These data will be used to study individual associations between diet and chronic diseases in three different European cultures. A topic of special interest is the effect of measurement error on the relation between diet and chronic diseases. Another topic to be dealt with in detail is the relation between diet and chronic non-specific lung diseases (CNSLD). Evidence is accumulating that nutritive and non-nutritive dietary anti-oxidants play a role in the etiology of CNSLD. The dietary data base of the Seven Countries Study provides the possibility to analyze these associations.

Since 1984 more than 2,300 men aged 65-84 in Finland, Italy, and the Netherlands have been examined in gerontologic surveys. Besides the traditionally collected data in the Seven Countries Study, information is also collected on: glucose tolerance, hemostatic factors, diet, physical activity, psycho-social variables, and different aspects of health. This provides a unique data set with information on risk factors and health in the elderly. Currently analyses are being carried out on:

- Functional status of the elderly.
- Development of a disability index.
- Predictive value of classical risk factors in the elderly.
- Relation between diet and health in the elderly.
- Physical activity and health in the elderly.
- Diet, glucose tolerance, and hyperinsulinemia in the elderly.
- Diet and hemostatic factors in the elderly.

These analyses should provide insight into the associations between risk factors and, not only chronic diseases, but also health in general (of great interest for aging populations). Nowadays, information on factors that influence *disease-free* life expectancy is most welcome by health policy makers and this type of information can only be obtained from prospective epidemiologic studies. The Seven Countries Study can play an important role in this context because the originally middle-aged

men have now been followed for 35 years, and much information has become and will become available on factors that influence health in old age.

There is still much to be learned about the causes of health and disease. The epidemiologic approach should therefore be broadened, as we have tried to do in the last decade. This was foreseen by Ancel Keys in the third monograph of the Seven Countries Study that appeared in 1980. We close by quoting the last paragraph of that monograph: 'The period of epidemiological exploration of these matters is not over, and there is still a lot to be learned from the study of the experiments of nature. The need for more and better epidemiological studies has never been more obvious. Until now, all prospective studies including the Seven Countries Study, have dealt with too few persons; the standard errors of the means and rates are too large. The instability of lifestyle in many populations greatly complicates the collection of representative data and their analyses, but perhaps the instability itself should be included in the analysis as a risk factor. Moreover, the almost universal assumption that risk is a linear function of the characteristics of interest must give way to less restrictive ideas and mathematical models. Finally, besides our great concern about the incidence of coronary heart disease, new epidemiological programs should be more broadly concerned with all disease and death.'

Picture of the authors taken at the international symposium 'Lessons for Science from the Seven Countries Study'. November 30, 1993, Fukuoka, Japan.
From left to right:
Upper row: H. Toshima, H. Blackburn, D. Kromhout, A. Menotti, A. Nissinen, S. Nedeljkovic, F. Epstein
Lower row: R. Buzina, C. Aravanis, A. Keys, F. Fidanza, M. Karvonen, A. Dontas

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Resident and Clinical and Research Associate, University of Health Sciences, Chicago Medical School, 1954-1960.
Senior Registar, Department of Cardiology, University of Athens, 1960-1962.
Associate Professor of Cardiology, University of Athens, 1963.
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Professor of Physiology and Biophysics (cardiology), University of Health Sciences, Chicago Medical School, 1973.
Director, Department of Cardiology, 'Evangelismos' Hospital Medical Center, Athens, 1975-1986.
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Special Experience

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Selected Publications

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Steering Committee, Coronary Drug Project, NHLBI, 1968-1975.
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Delta Omega, Honorary Society of Public Health, 1983.
Gold Heart Award, American Heart Association, 1990.
Ancel Keys Lecture, American Heart Association, 1991.
Research Achievement Award, American Heart Association, 1992.

Selected Publications

Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies. A classification system. Circulation 1960;21:1160.

Blackburn H. Brozek J, Taylor HL. Common circulatory measurements in smokers and nonsmokers. Circulation 1960;22:1091.

Rose GA, Blackburn H. Cardiovascular Survey Methods. WHO Monograph Series no. 56, WHO Press, Geneva, 1969.

Blackburn H. *Multifactor preventive trials in coronary heart disease.* In: Trends in epidemiology. Stewart GT (Eds). Thomas CC, Springfield, 1972.

Blackburn H. Diet, mass hyperlipidemia and coronary heart disease. A public health approach. In: Nutrition, Lipids and Coronary Heart Disease. Raven Press Publishers, New York, 1978.

Blackburn H. Determinants of individual and population blood lipoprotein levels: nutritional-genetic interactions. In: Genetic Factors in Nutrition. Velasques A, Bourges H (Eds). New York, Academic Press, 1984.

Blackburn H, Jacobs DR Jr. Physical activity and the risk of coronary heart disease. (Editorial) N Engl J Med 1988;319(18):1217-1219.

Blackburn H, Jacobs DR Jr. The ongoing natural experiment of cardiovascular disease in Japan. (Editorial) Circulation 1989;79:718-720.

Blackburn H. Community programme in CHD prevention and health promotion: Changing community behaviour. In: Coronary Heart Disease Epidemiology. From Aetiology to Public Health. Marmot M, Eliott P (Eds). Oxford University Press, 1991:495-514.

Blackburn H. The Ancel Keys Lecture. The three beauties: bench, clinical, and population research. Circulation 1992;86:1323-1331.

Van Buchem, Frans SP

Professor
Born November 30, 1897
Died August 1, 1979

Education

University of Leiden	M.D.	1921	Medicine
University of Leiden	Ph.D.	1924	

Professional Experience

Resident internal medicine, Klevarie Hospital, Maastricht, 1921-1925.
Chief Resident internal medicine, University of Groningen, 1925-1929.
Chief, Dept. internal medicine and Chief Physician, St Elisabeth Hospital, Tilburg, 1929-1945.
Professor internal medicine, University of Groningen, 1945-1959.

Special Experience

Resident, Dept. of Cardiology, Vienna, Austria, 1924.
Member of WHO international medical team, visits to: Calcutta (India), Rangoon (Burma), Calabo (Ceylon), 1952.
Principal Investigator, Zutphen Study, 1960-1974.

Committees and Offices

Member of the British Institute of Radiology, 1938.
Honorary member of the Cardiological Society of India, 1953.
Fellow of the American College of Chest Physicians, 1954
Member of the French Cardiologic Society, 1950.
Member of the Royal Dutch Academy of Science, 1958.
Member of the Netherlands Health Council, 1958.
Fellow International Angiological Society, 1963.
Honorary member of the Dutch Medical Society, 1968.
Member of the Belgium Cardiologic Society, 1968.
Member Council on Epidemiology and Prevention, International Society of Cardiology, 1968.

Editorial Boards

Netherlands Journal of Medicine (NTvG), 1951.
Acta Medica Scandinavica, 1951.

Selected Publications

Van Buchem FSP. Peptic ulcer of the greater curvature of the stomach. Br J Radiol 1939;11:667.

Van Buchem FSP, Nieveen J. The basis of the treatment of diabetes mellitus. Acta Med Scand 1952;142:190.

Van Buchem FSP. Dilatation of the pulmonary artery. Circulation 1956;8:719.

Van Buchem FSP. Primary aldosteronism due to adrenocortical hyperplasia. Lancet 1956;II:335.

Van Buchem FSP. The electrocardiogram and potassium metabolism. Am J Med 1957;23:376.

Van Buchem FSP, Pol G, De Gier J, Böttcher CJF, Pries C. Congenital β-lipoprotein deficiency. Am J Med 1966;40:794.

Van Buchem FSP, Dalderup LM. The town of Zutphen, the Netherlands. In: Epidemiological studies related to coronary heart disease: Characteristics of men aged 40-59 in seven countries. Keys A, *et al* (Eds). Acta Med Scand 1967;460 Suppl:191.

Van Buchem FSP. Zutphen, a town in the Netherlands. In: Coronary heart disease in seven countries. Keys A (Ed). Circulation 1970;41(Suppl 1):I-76.

Van Buchem FSP, Schermers TG, Van den Berg JW. The clinical significance of aortic sclerosis. Am Heart J 1970;80:831.

Van Buchem FSP. Hyperostosis corticalis generalisata. (Van Buchem's disease). Monograph Elsevier, Amsterdam, 1976.

Buzina, Ratko **Professor**

Education

Medical School University of Zagreb, Croatia	M.D.	1944	Medicine
School of Public Health, University Zagreb, Croatia	D.P.H.	1951-1953	Public health nutrition
University of Zagreb, Croatia	Sc.D.	1963	Medicine

Professional Experience

Chief, Community Health Services, 1947-1950.
Assistant Professor (Nutrition), Institute of Public Health Zagreb, Croatia, 1950-1956.
Associate Professor (Nutrition), Medical School, University of Zagreb, Croatia, 1956-1963.
Professor (Nutrition) Medical School, University of Zagreb, Croatia, 1963-present.
Chief, Nutrition Department, Institute of Public Health, Zagreb, Croatia, 1973-1985.

Special Experience

Postgraduate Training in Biochemistry and Vitaminology. Department of Biochemistry, Medical Faculty, University of Basel, Switzerland, 1950-1951.
Research Fellow, Laboratory of Physiological Hygiene, Medical School, University Minnesota, Minneapolis USA, 1955-1956.
Research Fellow, Department of Nutrition, Medical School Vanderbilt University, Nashville USA, 1956
Coordinator (Croatia) International Study on the Epidemiology of Coronary Heart Disease, 1958-1985.
Nutritional Advisor to the World Health Organization for South East Asia in New Delhi, India, 1959-1962.
WHO Short Term Consultant (Nutrition) to India, Burma, Sri Lanka and Thailand, 1963-1981.
Consultant (Nutrition) WHO Headquarters Geneva, Switzerland, 1989-present.

Committees and Offices

Member, Croatian Medical Association.
Member, Croatian Nutrition Society (President 1983-1987).
Member, American Society of Clinical Nutrition.
Member, American Institute of Nutrition.
Member, American Public Health Association.
Member, Hungarian Nutrition Society.
Member, International Society and Federation of Cardiology.
Board Member, International Society for Trace Element Research in Humans, 1986-present.
Member, Group of European Nutritionists (GEN) and Vice-president, 1988-present.
Member, World Health Organization Panel on Nutrition, 1963-present.
President, International Union of Nutrition Sciences, 1981-1985, Honorary President since 1985.
Member, Scientific Committee (Nutrition) of the Community Alpe-Adria.

Selected Publications

Brozek J, Buzina R, Mikic F. Population studies on serum cholesterol and dietary fat in Yugoslavia. Am J Clin Nutr 1957;5:279-285.

Buzina R, Keys A. Blood coagulation after a fat meal. Circulation 1956;14:854-858.

Keys A, Buzina R, Grande F, Anderson JT. The effects of meals of different fats on blood coagulation. Circulation 1957;15:214-219.

Buzina R, Ferber E, Keys A, Brodarec A, Agneletto B, Horvat A. Diets of rural families and heads of families in two regions of Yugoslavia. Voeding 1964;27:629-639.

Buzina R, Keys A, Brodarec A, Anderson JT, Fidanza F. Dietary surveys in rural Yugoslavia. II Chemical analysis of diets in Dalmatia and Slavonia. Voeding 1966;27:31-36.

Buzina R, Keys A, Brodarec A, Anderson JT, Fidanza F. Dietary surveys in rural Yugoslavia. III Comparison of three methods. Voeding 1966;27:99-105.

Buzina R, Keys A, Mohacek I, Hahn A, Brozek J, Blackburn H. Rural men in Dalmatia and Slavonia, Yugoslavia. In: Epidemiological studies related to coronary heart disease: Characteristics of men aged 40-59 in Seven Countries. Keys A *et al.* (Eds). Acta Med Scand 1967;460:147-168.

Buzina R, Keys A, Mohacek I, Marinkovic M, Hahn A, Blackburn H. In: Coronary Heart Disease in Seven Countries. Five-year follow-up in Dalmatia and Slavonia. Keys A (Ed). Circulation 1970;41(Suppl 1):40-51.

Buzina R, Suboticanec K, Saric M. Diet patterns and health problems: Diet in Southern Europe. Ann Nutr Metab 1991;(Suppl 1):32-40.

Buzina R. Recent evaluation of food habits in Mediterrarean populations. In: For a better nutrition in the 21th century. Leathwood P, Horrisberger M, James WPT (Eds) Nestle Nutr Workshop Series, Raven Press 1993;27:67-74.

Djordjević, Božidar Svetislav **Professor**
Born January 5, 1910
Died April 11, 1986

Education

Medical School, University of Belgrade	M.D.	1934	Medicine
Residency in Internal medicine,		1934-1938	
Training in Cardiology, Paris		1949	

Professional Experience
Assistant Professor, Internal Medicine, Medical Faculty Belgrade, 1936.
Associate Professor, Medical Faculty Belgrade, 1949.
Professor of Internal Medicine, Medical Faculty Belgrade, 1953.
Full Professor of Internal Medicine, Medical Faculty Belgrade, 1958.
Founder and Chief, Postgraduate School of Cardiology, Medical Faculty Belgrade, 1965-1978.
Deputy Dean, Medical Faculty Belgrade, 1952-1956.
Prorector and Rector, Belgrade University, 1957-1967.

Special Experience
Principal investigator and director of the Serbian part of the Seven Countries Study, 1962-1986.
Principal investigator 'Organization of cardiological health, research and educational service in Serbia', 1960-1970.
Director, Medical Research Institute, Serbian Academy of Science and Arts, 1962-1963.
Chief, Department of Internal Medicine, and Cardiological Team, 1952-1978.
Director, Medical Clinic B, 1974-1976.
Consultant, Institute of Cardiovascular Rehabilitation, Niška Banja, 1974-1986.
Board member for inauguration and opening of new medical faculties in Serbia: Novi Sad, Vojvodina, Pristina, Kosovo and Nish.
Associate to Full Member, Serbian Academy of Science and Arts, 1963-1986.

Committees and Offices
Secretary, Serbian Medical Society, 1946-1950.
Founder, Serbian Society of Cardiology, 1957.
General Secretary, Yugoslav Medical Associations, 1954-1960.
President, Yugoslav Medical Associations, 1960-1964.
Member, American College of Cardiology, 1963-1986.
Board Member, European Society of Cardiology.
Vice President, Yugoslav Society of Cardiology, 1957-1969.

Honors
Belgrade October Award. Contribution to science and arts for the realization of the Serbian part of the Seven Countries Study, 1970.
Serbian National Day Award 'Seventh of July'. Contribution to science and health promotion in Serbia.
Belgrade October Award. Contribution to science and arts for the monograph 'Congenital Heart Disease', 1974.
Decoration for 'Services to the people with golden wreath', 1965.
Brotherhood and Unity with Silver Wreath, 1970.
Medal of Labor with Red Flag, 1974.
Medal of the 'Legion of Honor' and medal 'Fenix' from France.
French International Cardiology Meetings (led by French cardiologist Camille Lian).

Selected Publications

Djordjević B., Nedeljković S. Variabilité des données electrocardiographiques dans trois groupes epidemiologiques differents (Recherches sur l'epidemiologie de la maladie coronaire). Actualités Cardiologiques et Angeiologiques Internationales 1965;14(4):281-286.

Djordjević B, Simić B, Simić A, Strasser T, Josipović V, Macarol V, Klinc I, Nedeljković S, Todorović P. Dietary studies in connection with epidemiology of heart diseases: results in Serbia. Voeding 1965;26:117-127.

Djordjević B, Josipović V, Strasser T, Nedeljković S, Lambić I, Balog B, Stojanović G, Macorol V, Simić B, Simić A, Slavković V, Milutinović P, Klinc I, Jovanović M: Les premiers resultats des recherches sur l'epidemiologie de la maladies coronaire dans trois groupes differants de population en Serbie. Actualités Cardiologiques et Angeiologiques Internationales 1966;15(1): 15-21.

Djordjević B, Josipović V, Nedeljković S, Strasser T, Slavković V, Simić B, Keys A, Blackburn H. Men in Velika Krsna, A Serbian village. In: Keys A, et al (Eds). Epidemiological studies related to coronary heart disease. Characteristics of men aged 40-59 in Seven Countries. Acta Scand 1967;Suppl 460:267-277.

Djordjević B, Balog B, Božinović LJ, Josipović V, Nedeljković S, Lambić I, Sekulić S, Slavković V, Stojanović G, Simić A, Simić B, Strasser T, Blackburn H, Keys A. Three cohorts of men followed five years in Serbia. In Keys A (Ed). Coronary heart disease in Seven Countries. Circulation 1970;41(Suppl 1):123-137.

Nedeljkovic S, Djordjevic B, Stojanovic G. Follow up ballistocardiographic findings in an epidemiological study of cardiovascular diseases in Yugoslavia, Ballistocardiography, Bibl Cardiol, Krager, Basel 1973;31:237-244.

Keys A, Aravanis C, Blackburn H, Djordjevic B, Dontas A, Fidanza F, Karvonen M, Menotti A, Taylor H. Lung function as a risk factor for coronary heart disease. Am J Publ Hlth 1972;62(11):1506-1511.

Keys A, Aravanis C, Blackburn H, Van Buchem FSP, Buzina R, Djordjevic B, Fidanza F, Karvonen M, Menotti A, Puddu V, Taylor H. Coronary heart disease: overweight and obesity as risk factors. Ann Intern Med 1972;77:15-27.

Keys A, Menotti A, Aravanis C, Blackburn H, Djordjević B, Buzina R, Dontas A, Fidanza F, Karvonen M, Kimura N, Mohachek I, Nedeljković S, Puddu V, Punsar S, Taylor H, Conti S, Kromhout D, Toshima H. The Seven Countries Study: 2.289 deaths in 15 years. Prev Med 1984;13:141-154.

Keys A, Menotti A, Karvonen M, Aravanis C, Blackburn H, Buzina R, Djordjević B, Dontas A, Fidanza F, Keys M, Kromhout D, Nedeljković S, Punsar S, Seccareccia F, Toshima H. The diet and 15 year death rates in the Seven Countries Study. Am J Epidemiol 1986;124(6):903-915.

Dontas, Anastasios S. **Professor**

Education

University of Athens, Greece	M.D.	1946	Medicine
University of Athens, Greece		1948	Physiology
University of Michigan	M.S.	1952	

Professional Experience

Head, Center of Studies of Age Related Changes in Man; Athens Home for the Aged, 1966-present.
Head, Department Medicine, Accident Hospital. Kifissia, 1970-1986.

Special Experience

Expert Adviser on problems of health of the elderly, WHO, 1984-1988.
Visiting Professor, University of Minnesota, 1978, 1982, 1989.
Chief (and Co-) Investigator for Greece for the following programmes:
The Seven Countries Study (NIH), 1960-1979.
Renal Function in the Aged, WHO, R/00073, 1965-1968.
Health Care of the Elderly (WHO), 1978-1981.
The Elderly in Eleven Countries (EEC), 1987-1989.

Committees and Offices

General Secretary, Hellenic Association Gerontology, 1977-present.
Chairman, Hellenic National Committee, World Assembly on Aging, UN, 1982.

Editorial Boards

Mechanisms of Aging and Development, 1972-1979.
International Journal of Technology and Ageing, 1989-present.
European Journal of Gerontology, 1991-present.
Geriatric Nephrology and Urology, 1991-present.

Honors

First Embiricos Award in Medicine (with associates Marketos SG, Papanayiotou P), 1970.
Academy of Athens Award for textbook 'The Third Age', 1984.
Second Don Goodchild Lecturer; 3rd National Symposium on Microbial Disease in Nephrology, London, 1985.
Sandoz Foundation of Gerontological Research Grantee, 1989.

Selected Publications

Dontas AS, Keys A, Anthopoulos L, Schulz N. Effects of age on the carotid pulse in two Greek populations. Circulation 1970;42:529-539.

Aravanis C, Corcondilas A, Dontas AS, Lekos D, Keys A. The Greek islands of Crete and Corfu. In: Coronary heart disease in seven countries. Keys A (Ed). Circulation 1970;41(Suppl 1): 88-100.

Papanayiotou P, Dontas AS. Waterloading test in bacteriuria. N Engl J Med 1972;287:531-534.

Dontas AS, Kasviki-Charvati P, Papanayiotou P, Marketos SG. Bacteriuria and survival in old age. N Engl J Med 1981;304:939-943.

Dontas AS, Jacobs D, Corcondilas A, Keys A, Hannan P. Longitudinal versus cross-sectional vital capacity changes and effecting factors. J Gerontology 1984;39:430-438.

Dontas AS, Paraskaki I, Petrikkos G, Giamarellou H. Diuresis bacteriuria in physically dependent elderly women. Age and Ageing 1987;16: 215-220.

Tzias V, Dontas AS, Petrikkos G, Papapetropoulou M, Dracopoulos H, Giamarellou H. Three-day antibiotic therapy in bacteriuria of old age. J Antimicr Chemother 1990;26:705-711.

Dontas AS, Tzonou A, Georgiades GL, Christakis G, Kasviki-Charvati P, Trichopoulos D. Survival in a residential home. J Am Geriatr Soc 1991; 39(7):641-649.

Dontas AS. Dilemmas of prolonging life of elderly patients in terminal system failure. Geriatric Nephrol Urol 1991;1:9-12.

Dontas AS, Giamarellou H, Staszewska-Pistoni M, Petrikkos G, Iakovou M, Tzias V. Short vs long cotrimoxazole courses in eradicating bacteriuria in the elderly. J Chemotherapy 1992;4:114-118.

Epstein, Frederick H — Professor

Education

University of Cambridge, England	B.A.	1940	Medicine
University of Cambridge, England	M.A.	1944	Medicine
University of Cambridge, England	M.B.Bchir	1944	Surgery
University of Cambridge, England	M.D.	1956	Medicine

Professional Experience

Resident Physician, England, 1943-1947.
New York University College of Medicine, 1948-1956.
Resident Lecturer, Research Associate, Associate Professor, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1956-1963.
Professor of Epidemiology, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1963-1973.
Professor of Preventive Medicine, University of Zurich, Switzerland, 1973-present.

Committees and Offices

Member, Royal College of Surgeons, London, 1943.
Chairman, Council on Epidemiology and Committee on Criteria and Methods, American Heart Association.
Member, Executive Committee, Council on Epidemiology and Prevention, International Society and Federation of Cardiology.
Editor, International Epidemiology Newsletter, International Society and Federation of Cardiology.
Director, Center for Research in Diseases of the Heart and Circulation and other disorders, University of Michigan, 1968-1973.
Member, Panel of Experts on Cardiovascular Diseases, World Health Organization, 1973-present.
Member, Committee on Epidemiology and Veterans Follow-up Studies, National Academy-National Research Council.
Member, Scientific Advisory Board, Swiss Society of Social and Preventive Medicine, 1979-present.
Member, Scientific Expert, Heart Special Projects Committee, National Heart, Lung and Blood Institute, 1978-1991.
Member, Task Force on Genetics, National Heart, Lung and Blood Institute.
Fellow, Royal College of Physicians, London, 1990.

Honors

Research Career Award, National Heart, Lung and Blood Institute, National Institutes of Health, 1962-1973.
Salomon Neuman Medal, German Society of Social Medicine.
MacArthur Postgraduate Lecture, University of Edinburgh, 1965.
George C. Griffith Scientific Lecture, Los Angeles, 1971.
Doctor Honoris Causa, University of Heidelberg, Germany, 1979.
Thomas Francis Jr. Memorial Lecture, University of Michigan, 1982.
Ancel Keys Lecture, American Heart Association, 1993.

Editorial Boards

Circulation
American Journal of Epidemiology
Atherosclerosis
Preventive Medicine
Sozial-und Praeventivmedizin (Swiss Journal of Social-and Preventive Medicine)
Nutrition Metabolism and Cardiovascular Disease
Cardiology
Cor et Vasa

Selected Publications

Epstein FH, Boas EP, Simpson R. The epidemiology of atherosclerosis among a random sample of clothing workers of different ethnic origins in New York City. J Chron Dis 1957;5:300,329.

Epstein FH. The epidemiology of coronary heart disease; a review. J Chron Dis 1965;18:735.

Epstein FH, Ostrander LD, Johnson BC, *et al.* Epidemiological studies of cardiovascular disease in a total community; Tecumseh, Michigan. Ann Int Med 1965;62:1170.

Epstein FH. Hyperglycemia - a risk factor in coronary heart disease. Circulation 1967;36:609.

Epstein FH. Coronary heart disease epidemiology revisited - clinical and community aspects. Circulation 1973;48:185.

Epstein FH. Preventive trials and the diet-heart question: wait for results or act now? Atherosclerosis. 1977;26:515.

Epstein FH, Holland WW. Prevention of chronic diseases in the community - one-disease versus multiple disease strategies. Int J Epidemiol 1983;12:135.

Epstein FH. Cholesterol, coronary heart disease, cancer and diet. Atherosclerosis Rev 1983;11:1-28.

Epstein FH, Pyörälä K. Perspectives for the primary prevention of premature coronary heart disease. Cardiology 1987;74:316.

Epstein FH. Low serum cholesterol, cancer and other non-cardiovascular diseases. Atherosclerosis 1992;94:1.

Fidanza, Flaminio **Professor**

Education

University of Naples (Italy)	M.D.	1945	Medicine

Professional Experience

Assistant Professor, Institute of Biochemistry, Medical School, University of Naples (Italy), 1946-1955.
Rockfeller Fellow, Laboratory of Physiological Hygiene, University of Minnesota, 1952-1953.
Assistant Professor, Institute of Human Physiology, Medical School, University of Naples, 1955-1965.
Professor in charge of Nutrition and Food Science, Medical School, University of Naples, 1961-1964.
Full Professor of Nutrition and Food Science, 1965-1990; Outside of tenure until retirement, 1990-present;
Director, 1965-present, Institute of Nutrition and Food Science, Faculty of Pharmacy, University of Perugia.

Special Experience

Principal Investigator, Italian Section, Seven Countries Study, 1958-1967.
Member, Food and Agriculture Organization Expert Working Groups, 1977, 1979, 1981, 1985.
Member, World Health Organization Expert Working Groups, 1977, 1979, 1981, 1985.

Committees and Offices

Member, Committee on Diabetes and Cardiovascular Diseases, International Union of Nutritional Sciences (IUNS), 1968-1972.
Member, Commission on Nutrition Education and Training, IUNS, 1970-1975.
Chairman, Commission on Nutritional Education and Training, IUNS, 1975-1982.
Permanent Representative of IUNS to FAO, 1972-1990.
Secretary General, Group of European Nutritionists, 1971-1978.
Vice-President and President, Group of European Nutritionists, 1978-1988.
President, Italian Association of Clinical and Preventive Nutrition, 1986-present.
Editorial Boards
Nutritio et Dieta, 1966-1976.
International Journal for Vitamin and Nutrition Research, 1971-present.
Progress in Food and Nutrition Science, 1975-1981.
Diabetes, Nutrition & Metabolism, 1988-present.
Nutrition, Metabolism and Cardiovascular Diseases, 1991-present.
Italian Journal of Clinical and Preventive Nutrition, editor, 1991-present.

Honors

Pavesi Award in Nutrition Research, 1964.
Diploma of Merit of School, Culture and Art of Italian Republic, 1986.

Selected Publications

Fidanza F, Keys A, Anderson JT. Density of body fat in man and other mammals. J Appl Physiol 1953;6:252-256.

Keys A, Fidanza F, Scardi V, *et al.* Studies on serum cholesterol and other characteristics on clinically healthy men in Naples. Arch Intern Med 1954;93:328-336.

Fidanza F, Fidanza-Alberti A, Ferro-Luzzi G, Proja M. Dietary surveys in connection with the epidemiology of heart disease: Results in Italy. Voeding 1964;25:502-509.

Fidanza F. Diets and dietary recommendations in ancient Greece and Rome and the school of Salerno. Prog Food Nutr Sci 1979;3:79-99.

Farchi G, Mariotti S, Menotti A, Seccareccia F, Torsello S, Fidanza F. Diet and 20-year mortality in two rural population groups of middle-aged men in Italy. Am J Clin Nutr 1989; 50:1095-1103.

Fidanza F. The Mediterranean Italian diet: Keys to contemporary thinking. Proc Nutr Soc 1991;50:519-526.

Fidanza F (Ed). Nutritional status assessment. A manual for population studies. Chapman & Hall, London 1991.

Borrelli R, Simonetti MS, Fidanza F. Inter- and intra-individual variability in food intake of elderly people in Perugia (Italy). Brit J Nutr 1992;68:3-10.

Farchi G, Fidanza F, Mariotti S, Menotti A. Alcohol and mortality in the Italian rural cohorts of the Seven Countries Study. Int J Epidemiol 1992;21:74-81.

Fidanza F. Nutrition and cardiovascular risk: The biological markers of dietary intake. Bibl Nutr Diet 1992;49:59-65.

Karvonen, Martti J. **Professor, Major General MC**

Education

Helsinki University	M.D.	1945	Medicine
University of Cambridge	Ph.D.	1950	Physiology
Specialist in Clinical Physiology		1964	
Specialist in Occupational Health		1970	

Professional Experience

Demonstrator, Institute of Physiology, Helsinki University, 1945-1950.
Lecturer of Sport Medicine, Institute of Physiology, Helsinki University, 1950-1956.
Director, Department of Physiology, Institute of Occupational Health, Helsinki, 1950-1967.
Docent of Physiology, Helsinki University, 1951-1968.
Surgeon General of the Air Force, 1956-1966.
Professor of Physiology, College of Veterinary Medicine, Helsinki, 1966-1970.
Director, Institute of Occupational Health, Helsinki, 1970-1974.
Surgeon General of the Armed Forces of Finland, 1974-1978.

Special Experience

Principal Investigator, The Finnish East-West Project of the Seven Countries Study, 1956-1980.
Regional Officer for Occupational Health and Rehabilitation, WHO Regional Office for Europe, Copenhagen, 1966-1967.
Visiting Professor, University of Dortmund, 1978-1980.
WHO Consultant:
Egypt, 1981,
Indonesia 1981, 1983,
WHO Regional Office for the Eastern Mediterranean, Alexandria, 1982,
WHO Headquarters, Geneva, for the MONICA Project, 1982-1983.
UN Consultant for Occupational Health in Poland, 1972.

Committees and Offices

President, Finnish Society for Sports Medicine, 1957-1962.
Member, Expert Advisory Panel on Cardiovascular Diseases, WHO, 1962-present.
President, Finnish Medical Association, 1963-1965, 1969.
Rector, College of Veterinary Medicine, Helsinki, 1969-1970.
Vice-President, Finnish Heart Association, 1971-1975.
Chairman, State Board on Clean Air and Noise Protection, 1973-1974.
President, Finnish Society for Research in Sports Sciences, 1975-1977.
Chairman, State Committee in Health Education, 1975-1976.

Editorial Boards

American Journal of Cardiology, 1958-1967.
Scandinavian Journal of Work, Environment and Health, 1972-1984.
Scandinavian Journal of Sports Sciences, Editor in Chief, 1979, Editorial Board, 1980-1989.
International Archives of Occupational and Environmental Health, 1979-1986.
European Journal of Applied Physiology, 1980-1984.

Honors

Ruhemann-plaquette, German Association of Sports Medicine, 1966.
Corresponding Member, German Association for Occupational Health, 1972-present.
Doctor Honoris Causa, Helsinki University, Helsinki, Finland, 1981.
Doctor Honoris Causa, Jyväskylä University, Jyväskylä, Finland, 1982.
Honor Award, American College of Sports Medicine, 1991.
Honorary memberships:
J. Purkinje Medical Society, Czechoslovakia, 1961.
Finnish Society for Sports Medicine, 1969.
Finnish Medical Association, 1978.
Finnish Aerospace Medical Association, 1984.
Finnish Sauna Society, 1988.
Finnish Cardiological Society, 1988.
Finnish Society for Clinical Physiology, 1993.

Selected Publications

Jokl E, Karvonen MJ, Kihlberg J, Koskela A. Sports in the cultural pattern of the world. Helsinki: Institute of Occupational Health, 1956, 116 pp.

Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate. Ann Med Exp Biol Fenn 1957;35:307-315.

Karvonen MJ, Telivuo LJ, Järvinen EJK. Sphygmomanometer cuff size and the accuracy of indirect measurement of blood pressure. Am J Cardiol 1964;13:688-693.

Hasan J, Karvonen MJ, Piironen P. Physiological effects of extreme heat as studied in the Finnish 'sauna' bath. Part I. Am J Phys Med 1966;45:296-314. Part II. Am J Phys Med 1967;46:1227-1245.

Pyörälä K, Karvonen MJ, Taskinen P, Takkunen J, Kyrönseppä H, Peltokallio P. Cardiovascular studies on former endurance athletes. Am J Cardiol 1967;20:191-205.

Karvonen MJ, Klemona H, Virkajärvi J, Kekkonen A. Longevity of endurance skiers. Med Sci Sports 1974;6:49-51.

Turpeinen O, Karvonen MJ, Pekkarinen M, Miettinen M, Elosuo R, Paavilainen E. Dietary prevention of coronary heart disease: The Finnish Mental Hospital Study. Int J Epidemiol 1979;8:99-118.

Karvonen MJ. Physical activity and cardiovascular morbidity. Scand J Work Environ Health 1984;10:389-395.

Karvonen MJ, Mikheev MI (Eds). Epidemiology of Occupational Health. Copenhagen. World Health Organization, Regional Office for Europe, 1986:1-392.

Karvonen MJ. Determinants of cardiovascular diseases in the elderly. Ann Med 1989; 21:3-14.

Keys, Ancel — Professor/Director

Education

University of California, Berkely, USA	B.A.	1924	Biology
University of California, Berkely, USA	M.A.	1928	Biology
University of California, Berkely, USA	Ph.D.	1930	Biology
Kings College, Cambridge, UK	Ph.D.	1936	Physiology

Professional Experience

US National Research Fellow in Copenhagen, 1930-1931.
Rockefeller Foundation Fellow in King's College, Cambridge University, 1931-1932.
Instructor of Physiology Cambridge University, 1932-1933.
Instructor in Biochemistry Harvard University 1933-1936.
Staff member, Mayo Clinic 1936-1937.
Assistant Professor, Associate professor, Professor of Physiology, University of Minnesota, Medical School, 1937-1940.
Professor and Director Laboratory of Physiological Hygiene, University of Minnesota, School of Public Health 1940-1972.
Professor emeritus 1972-present.

Special Experience

Special Assistant to the Secretary of Defense, 1939-1943.
Visiting Professor Magdalen College, Oxford University 1951-1952.
Visiting Professor Department of Physiology Naples University 1963-1964.

Committees and Offices

Chairman, Committee on Food and Nutrition, Food and Agriculture Organization, World Health Organization, 1951.
Chairman, Research Committee, International Society of Cardiology, 1954-1958.

Honors

Honorary citizen of Gioia Tauro and of Nicotera, Italy.
Member Academy of Finland.
The American Heart Association established the annual Ancel Keys lectureship in 1989.
Bristol Meyers Squibb award for research in nutrition, 1993.

Selected Publications

Keys A. Physical performance in relation to diet. Fed Proc 1943;2:164-187.

Keys A, Brozek J, Henschel A, Mickelson O, Taylor HL. The biology of human starvation. Minneapolis MN, University of Minnesota Press, Minneapolis, MN, 1950:Vol. 1-2:1-1385.

Keys A. The cholesterol problem. Voeding 1952;13:539-555.

Keys A, Brozek J. Body fat in adult man. Physiol Rev 1953;33:245-325.

Keys A, Anderson JT, Grande F. Prediction of serum cholesterol responses of man to changes in fats in the diet. Lancet 1957;2:959-966.

Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet. IV. Particular saturated fatty acids in the diet. Metabolism 1965;14:776-787.

Keys A, Blackburn HW, Van Buchem FSP, Buzina R, Djordjević BS, Dontas AS, Fidanza F, karvonen MJ, Kimura N, Lekos D, Monti M, Puddu V, Taylor HL. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in Seven Countries. Acta Med Scand 1967;460(Suppl 180):1-392.

Keys A. Coronary heart disease in Seven Countries. Circulation 1970;41(Suppl 1):1-211.

Keys A, Aravanis C, Blackburn H, Buzina R, Djordjević BS, Dontas AS, Fidanza F, Karvonen MJ, Kimura N, Menotti A, Mohachek I, Nedeljković S, Puddu V, Punsar S, Taylor HL, Van Buchem FSP. Seven countries. A multivariate analysis of death and coronary heart disease. A Commonwealth Fund Book, Harvard University Press, Cambridge Mass and London, 1980:1-381.

Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjević BS, Dontas AS, Fidanza F, Keys M, Kromhout D, Nedeljković S, Punsar S, Seccareccia F, Toshima H. The diet and 15-year death rate in the Seven Countries Study. Am J Epidemiol 1986;124: 903-915.

Kimura, Noboru

Professor
Born August 4, 1911
Died September 9, 1983

Education

Kyushu University, Faculty of Medicine	M.D.	1936	Medicine

Professional Experience

Resident, the 1st Department of Internal Medicine, Kyushu University Hospital, 1936.
Fellow, the 1st Department of Internal Medicine, Kyushu University Hospital, 1942.
Lecturer, the 1st Department of Internal Medicine, Kyushu University, 1943.
Associate Professor, the 1st Department of Internal Medicine, Kyushu University, 1945.
Professor, Kyushu University Medical College, 1945.
Exchange Research Fellow, Rockefeller Foundation, 1951.
Lecturer, the 3rd Department of Internal Medicine, Kurume University School of Medicine, 1957.
Professor, the 3rd Department of Internal Medicine, Kurume University School of Medicine, 1958-1977.
Director, the Institute of Cardiovascular Diseases, Kurume University School of Medicine, 1959-1977.
Dean, Kurume University School of Medicine, 1972-1973.
Vice-president, Saga Medical College, 1976-1979.
President, Kurume University, 1980-1982.

Special Experience

Member, Seven Countries Study Group
Member, WHO Professional Consultant Committee, 1955.
Visiting Lecturer, Department of Internal Medicine, Kyushu University, 1958.
Member, Science Council of Japan, 1969.
Member, Board of Directors, Japan Heart Foundation, 1970-1983.
Vice-president, the 1st South-East Asian Conference of Cardiovascular Disease Prevention, 1973.
Member, National Survey on Chronic Non-communicable Disorders of Adult Population, 1971.
President, Kimura Memorial Heart Foundation, 1977.

Committees and Offices

President, the 32nd Scientific Session, Japanese Circulation Society, 1968.
President, the 14th Scientific Session, Japanese Society of Rheumatic Disease, 1970.
President, the 11th Scientific Session, Japanese Society of Medical Electronics, 1971.
Member, Organizing Committee, International Society of Nutrition, 1974.
Director, Japan Atherosclerosis Society, 1974.
Vice-president, the 8th World Congress of Cardiology, 1975.
Chairman, Society of Human Dock, 1975.
President, the 75th Scientific Session, Japanese Society of Internal Medicine, 1976.
President, the 11st Scientific Session, Japanese Association for Cerebro-Cardiovascular Disease Control, 1976.
Chairman, Executive Committee of Asian-Pacific Hypertension Conference, 1976.

Honors

Japan Medical Association Award, 1976.
Honorary Professor, Kurume University, 1977.

Selected Publications

Kimura N, Fukumura I, Nawata Y, Oishi K, Matsumoto M, Masaki H, Utsu N, Kawazoe K, Toshima H, Mori F, Mori I, Shikata H, Fukumoto A, Akasu M, Nakakura S. Electrocardiographic and vectorcardiographic studies of proved mitral valvular disease. Jpn Circ J 1961;25:872.

Kimura N, Toshima H, Nakakura S, Fukumoto A, Akasu M, Yamaguchi K. The component of right ventricular hypertrophy in QRS complexes. Observation on electrocardiographic changes after commissurotomy in pure mitral stenosis. Jpn Circ J 1962;26:885.

Kimura N, Ueda H, Donomae I, Kimura E, Maekawa M, Niitani H, Okinaka S, Saito M, Sano T, Tasaka S, Takatsu T, Takayasu M. Prognostic value of various electrocardiographic features. The report of the committee on the criteria of the heart disease and electrocardiogram. Jpn Heart J 1963;4:239.

Kimura N, Toshima H. Essential differences between vectorcardiogram and electrocardiogram. Jpn Circ J 1963;27:61.

Kimura N, Toshima H, Mori F, Kodama A, Abe K, Outsuka Y, Arima T, Oki Y, Yokota Y. Studies on the metabolism of carbohydrate, lipids and contractile protein in myocardium and on the hemodynamics in the dogs with experimentally produced aortic valvular lesions. Jpn Circ J 1967;31:1916.

Kimura N, Toshima H, Takayama K, Nakayama Y, Abe K, Matoba T. Comparative study of angiogram, electrocardiogram and vectorcardiogram on the disease with left ventricular diastolic loading. Jpn Circ J 1967;31:1878.

Kimura N, Keys A. Rural Southern Japan. In: Coronary heart disease in seven countries. Keys A (Ed). Circulation 1970;41(Suppl 1):101.

Kimura N, Toshima H, Takayama K, Shimada S, Soejima K. Clinical usefulness of the vectorcardioagraphic pattern difference using the Kimura- and Frank-Lead System. Jpn J Med 1971;10:50.

Kimura N, Toshima H, Nakayama Y, Mizuguchi T, Takayama K, Yoshinaga M, Fukami T, Tashiro H, Katayama F, Abe K, Arima T, Yokota Y, Minagawa E, Tanaka R, Akiyoshi T, Soejima K, Yamada K, Mizunoe A, Nakamura K, Oshima F, Tanaka K, Akusu K, Niizaki T, Ikeda H, Nakamichi E, Ageta M, Miike Y, Inoue T, Nakagawa T, Nanbu S, Tanioka T, Shimada S, Fukumoto T. Epidemiological study on cerebro and cardiovascular disease in Tanushimaru and Ushibuka. Jpn J Med 1972;11:62.

Kimura N. Epidemiological studies in Japan on smoking and cardiovascular diseas. Volume 2 of the proceeding of the 3rd World Conference on smoking and health (USA). Department of Health, Education, and Welfare. DHEW Publication no (NIH) 1977;77-1413:185-198.

Kromhout, Daan — Director/Professor

Education

Agricultural University Wageningen, NL	M.Sc.	1974	Human nutrition
Agricultural University Wageningen, NL	Ph.D.	1978	Human nutrition
University of Minnesota,Minneapolis, MN	M.P.H.	1981	Epidemiology

Professional Experience

Research Assistant, Dept. Hematology, Karolinska Hospital, Stockholm, Sweden, 1972.
Ph.D. student, Dept. Human Nutrition Agricultural University Wageningen, Netherlands, 1974-1978.
Assistant Professor, Dept. of Social Medicine, University of Leiden, Netherlands, 1977-1982.
Associate Professor, Dept. of Social Medicine, University of Leiden, Netherlands, 1982-1988.
Professor in Nutritional Epidemiology, University of Leiden, Netherlands, 1984-present.
Head, Department of Epidemiology, National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands, 1988-1991.
Director, Division of Public Health Research, National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands, 1991-present.

Special Experience

Principal Investigator of the Zutphen Study, 1978-present.
Member Executive Committee of the INTERSALT study, 1982-1988.
Member Executive Committee of the Seven Countries Study, 1986-present.
Visiting Professor University of Helsinki, 1987.
Principal Investigator of the Monitoring Project on Cardiovascular Diseases in the Netherlands, 1987-1992.
Principal Investigator of the scenario project on chronic diseases, 1988-1992.
Temporary Advisor of the WHO study group on 'Diet, nutrition and prevention of non-communicable diseases', 1989.

Committees and Offices

Member, Committee on Nutrition and Atherosclerosis. Nutrition Council, 1978-1982
Member, Committee on Diet and Coronary Heart Disease, Nutrition Council, 1979-1982.
Member, Committee on Diet and Cancer, Nutrition Council, 1982-1986.
Chairman, Foundation Quality Control Chemical Analyses, 1986-1990.
Member, Nutrition Council, 1984-present.
Member and Vice-Chairman, Committee Socio-economic Health Differences, 1987-present.
Chairman, Committee Nutritional Surveillance, Nutrition Council, 1988-1992.
Secretary and Chairman, Working group Nutrition of the Netherlands Organization for Research, 1991-present.

Honors

Travel Grant Netherlands Organization for Scientific Research for one-year stay at the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, MN, USA, 1980.
Liga Nutrition Award of the Netherlands Nutrition Foundation, 1989.
Annie B. Cunning lecture, Royal Australasian College of Physicians, Melbourne, 1990.
Keynote lecture, Tercentenary Charter Celebration, Royal College of Physicians of Ireland, Dublin, 1992.

Selected Publications

Kromhout D, Bosschieter EB, De Lezenne Coulander C. Dietary fibre and 10-year mortality from coronary heart disease, cancer and all causes. The Zutphen Study. Lancet 1982;II: 518-522.

Arntzenius AC, Kromhout D, Barth JD, Reiber JHC, Bruschke AVG, Buis B, Van Gent CM, Kempen-Voogd N, Strikwerda S, Van der Velde EA. Diet, lipoproteins and coronary lesion growth. The Leiden Intervention Trial. N Engl J Med 1985;312:805-811.

Kromhout D, Bosschieter EB, De Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312: 1205-1209.

Kromhout D. Essential micronutrients in relation to carcinogenesis. Am J Clin Nutr 1987;45: 1361-1367.

Kromhout D, Bosschieter EB, Drijver M, De Lezenne Coulander C. Serum cholesterol and 25-year incidence of and mortality from myocardial infarction and cancer. The Zutphen Study. Arch Intern Med 1988;148:1051-1055.

Kromhout D, Keys A, Aravanis C, Buzina R, Fidanza F, Giampaoli S, Jansen A, Menotti A, Nedeljkovic S, Pekkarinen M, Simic BS, Toshima H. Food consumption patterns in the nineteen sixties in Seven Countries. Am J Clin Nutr 1989;49:889-894.

Kromhout D, Nissinen A, Menotti A, Bloemberg B, Pekkanen J, Giampaoli S. Total and HDL cholesterol and their correlates in elderly men in Finland, Italy and the Netherlands. Am J Epidemiol 1990;131:855-863.

Caspersen CJ, Bloemberg BPM, Saris WHM, Merritt RK, Kromhout D. The prevalence of selected physical activities and their relationship with coronary heart disease risk factors in elderly men: The Zutphen Study, 1985. Am J Epidemiol 1991;133:1078-1092.

Kromhout D. Dietary fats. Longterm implications for health. Nutr Rev 1992;50(II):49-53.

Kromhout D, Bloemberg BPM. Methods in nutritional epidemiology. In: Coronary heart disease epidemiology: From aetiology to public health. Marmot M, Elliott P (Eds). Oxford University Press 1992:140-151.

Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease. (The Zutphen Elderly Study). Lancet 1993;342:1007-1011.

Menotti, Alessandro — Director/Professor

Education

University of Rome, Italy	M.D.	1958	Medicine
University of Turin, Italy		1960	Cardiology
University of Rome, Italy		1963	Pathology
London School of Hygiene, London, UK		1964/1967	Medical statistics
University of Rome, Italy	Ph.D.	1971	Health statistics

Professional Experience

Assistant, Department of Medicine, Government Hospital of Tripoli, Libya, 1960-1961.
Research Associate, Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis Minnesota, USA, 1962-1975
Assistant, Center for Cardiovascular Diseases, St.Camillo Hospital, Rome, Italy, 1975-1979.
Director, Unit for Chronic Diseases, Laboratory of Epidemiology and Biostatistics, Istituto Superiore di Sanità (National Institute of Health), Rome, Italy, 1979-1989.
Director, Laboratory of Epidemiology and Biostatistics, Istituto Superiore di Sanità (National Institute of Health), Rome, Italy, 1989-present.

Special Experience

Member of the Central Staff, Seven Countries Study on Cardiovascular Diseases, 1967-1993.
Principal Investigator, Death Rates among Italian Railroad Employees, NIH Grant, 1968-1976.
WHO MONICA Project (Monitoring Cardiovascular Diseases), Coordinator for Italy, 1981-1993; Member Steering Committee, 1981-1983.
Principal Investigator, WHO European Multifactor Preventive Trial of CHD,1973-1988.
WHO ERICA Project (European Risk Factor Coordinated Analysis), Member Steering Committe, 1982-1993.
Lecturer on Epidemiology, University of Rome, Italy 1972-1979, 1981-1983, and University of Padua at Verona, Italy, 1974.

Committees and Offices

Temporary Adviser in more than 40 Working Groups of the World Health Organization, 1966-1990.
Consultant to the Health Service, Italian Railroad System, 1978-1993.
Responsible for Cardiovascular Diseases in the Report on the Nation's Health Status of the Italian Ministry of Health, 1981-1984,1989.
Italian Representative in the Committee on Epidemiology of the European Community, Bruxelles, 1981-1982.
Member of the National Committee for Cardiology and Cardiac Surgery of the Italian Ministry of Health, 1981-1993.
Co-Director, Decentralized Activities for Epidemiology and Prevention of Cardiovascular Diseases of the World Health Organization, Regional Office for Europe, at University of Heidelberg, Germany, 1982-1989.
Member of the Working Group on Guidelines for the Italian Diet, Italian National Institute of Nutrition, 1985-1986.
Coordinator Sub-Project Community Medicine in the Targeted Project on Preventive Medicine, Italian National Research Council, 1989-1993.
Vice-Chairman Section on Epidemiology and Prevention, International Society and Federation of Cardiology, 1978-1982, and Member at large, Executive Committee, 1990-1993.

Committees and Offices Continued

Vice-Chairman, Working Group on Epidemiology and Prevention, European Society of Cardiology, 1983-1986.

Chairman, GIEP (Italian Group for Epidemiology and Prevention Cardiovascular Diseases), 1983-1986.

Editorial Boards

Bollettino Società Italiana di Cardiologia, 1962-1968;

Cuore e Circolazione,1962-1970;

Giornale Italiano di Cardiologia, 1971-1979.

Selected Publications

Menotti A, Moschini-Antinori E, Splendiani G. Heart diseases in Tripolitania. A clinical and statistical study. Malat Cardiov 1963;4:665-675.

Puddu V, Menotti A. Ischemic heart disease and cerebrovascular accidents mortality trends in the Italian regions. Their relationship to some socio-economic indexes. Acta Cardiol 1966;21:585-591.

Menotti A, Capocaccia R, Conti S, Farchi G, Mariotti S, Verdecchia A, Keys A, Karvonen MJ, Punsar S. Identifying subsets of major risk factors in multivariate estimation of coronary risk. J Chron Dis 1977;30:557-565.

Research Group ATS-RF2 of the Italian National Research Council (A Menotti among the authors). Time trends of some cardiovascular risk factors in Italy. Am J Epidemiol 1987;126:95-103.

Menotti A, Keys A, Blackburn H, Aravanis C, Dontas AS, Fidanza F, Giampaoli S, Karvonen MJ, Kromhout D, Nedeljković S, Nissinen A, Pekkanen J, Punsar S, Seccareccia F, Toshima H. Twenty-year mortality and prediction of stroke in twelve cohorts of the Seven Countries Study. Int J Epidemiol 1990;19:309-315.

Menotti A, Keys A, Kromhout D, Nissinen A, Blackburn H, Fidanza F, Giampaoli S, Karvonen MJ, Pekkanen J, Punsar S, Seccareccia F. Twenty-five year mortality from coronary heart disease and its prediction in five cohorts of middle aged men in Finland, the Netherlands and Italy. Prev Med 1990;19:270-278.

ERICA Research Group (A Menotti among the authors). Prediction coronary heart disease in Europe. The 2nd report of the WHO-ERICA Project. Eur Heart J 1991;12:291-297.

Menotti A, Keys A, Blackburn H, Karvonen M, Punsar S, Nissinen A, Pekkanen J, Kromhout D, Giampaoli S, Seccareccia F, Fidanza F, Nedeljković S, Aravanis C, Dontas AS, Toshima H. Blood pressure changes as predictors of future mortality in the Seven Countries Study. J Hum Hypertension 1991;5:137-144.

Menotti A, Lanti P, Seccareccia F, Giampaoli S, Dima F. Multivariate prediction of the first major cerebrovascular event in an Italian sample of middle aged men followed-up for 25 years. Stroke 1993;24:42-48.

Menotti A, Seccareccia F, Lanti M, Giampaoli S, Dima F. Time changes in predictability of coronary heart disease in an Italian aging population. Cardiology 1993;82:172-180.

Nedeljkovic, Srećko **Professor**

Education

Medical School, University of Belgrade	M.D.	1952	Medicine
Residency and specialty in internal medicine		1953-1957	
Colombia University, NY		1961-1962	Biostatistics
Habilitation in medical sciences on ballistocardiography		1963	
Subspecialty in cardiology, Medical Faculty, Belgrade		1965	Cardiology
Master of Science	M.Sc.	1967	
Doctor of science	Ph.D	1969	

Professional Experience

Assistant Professor of Internal Medicine, Medical Faculty Belgrade, 1959.
Associate Professor, 1970 and Professor, 1976.
Full Professor of Internal Medicine and Cardiology, 1981-1989

Special Experience

Project Officer, Serbian cohorts of the Seven Countries Study, 1962-1985
Principal Investigator, Serbian part of the Seven Countries Study, 1986-1993.
Co-investigator, the Belgrade 'Rakovica cardiovascular study', 1972-1992.
Principal Investigator, 'Electrotherapy in cardiac arrhythmias', Serbian Research Council, 1964-1972.
Principal Investigator, 'Hemodynamics in coronary heart diseases', Serbian Research Council, 1974-1980.
Secretary and Chief, Postgraduate School of Cardiology, 1975-1989.
Founder and Chief, Cardiology Laboratory, Medical Clinic B, 1962-1984.
Chief, Cardiology Clinic at Medical clinic B, 1985-1986.
Founder and First Director, Institute of Cardiovascular Diseases, University Clinical Centre, Medical Faculty Belgrade, 1987-1989.
Consultant, Institute of Cardiovascular Diseases, University Clinical Centre, 1989-present.

Committees and Offices

Member, Serbian Medical Academy, 1978. Vice-president, 1990-1993.
President, Serbian Society of Cardiology, 1976-1978.
President, Yugoslav Society of Cardiology, 1985-1989. Honorary president since 1992.
Member, Scientific Committee of Mediterranean Association of Cardiology and Cardiac Surgery, 1987-present.
Affiliated Fellow American College of Cardiology, 1965-1992. Present status emeritus.
Fellow, European Society of Cardiology, since 1988.
Organizer, two cardiology exchange meetings between Baylor College of Medicine (Houston, TX) and Belgrade Medical Faculty. In Belgrade, 1981 and in Houston, 1991.
Chairman, Symposium 'Rheumatic heart disease in young' World Congress of Cardiology, Moscow, 1982.

Honors

Belgrade October Award. Contribution to science and arts, for the realization of the Serbian part of the Seven Countries Study, 1970.
Serbian National Day Award 'Seventh July' for the contribution to science and health promotion, in relation with the 'Rakovica cardiovascular study', 1979.
Belgrade October Award. Contribution to science and arts, for the monograph 'Cardiac block and pacemakers', 1981.
Decoration for 'Services to the people with golden wreath', 1986.
Gold Medal for Services to Yugoslav Society of Cardiology, 1989.
'Yugoslav Distinguished Sportsman title for chess play achievements and two silver medals won in European championships, 1958 and 1961.
Serbian Medical Society 'Life achievement award', 1993

Selected Publications

Plavšič Č, Ilić M, Nedeljković S. Les maladies des arteres coronaires en Yougoslavie. Acta Cardiologica 1959;14(Suppl 8):79-86.

Djordjević B, Simić B, Simić A, Strasser T, Josipović V, Macarol V, Klinc I, Nedeljković S, Todorović P. Dietary studies in connection with epidemiology of heart diseases: results in Serbia. Voeding 1965;26:117-127.

Nedeljković S, Djordjević B, Stojanović G. Ballistocardiographic findings in an epidemiological study of cardiovascular diseases in Yugoslavia, Ballistocardiography, Bibl Cardiol, Krager, Basel 1968;21:16-20.

Djordjević B, Balog B, Božinović Lj, Josipović V, Nedeljković S, Lambić I, Sekulić S, Slavković V, Stojanović G, Simić A, Simić B, Strasser T, Blackburn H, Keys A. Three cohorts of men followed five years in Serbia. In Keys A, *et al* (Eds). Coronary heart disease in Seven Countries. Circulation 1970;41 (Suppl 1): 123-137.

Nedeljković S, Djordjević B, Stojanović G. Follow up ballistocardiographic findings in an epidemiological study of cardiovascular diseases in Yugoslavia, Ballistocardiography, Bibl Cardiol, Krager, Basel 1973;31:237-244.

Nedeljković S, Djordjević B, Josipović V, Božinović Lj, Kozarević Dj, Demirović J, Vojvodić N, Simin N, Ostojić M, Grujić M, Milošević M. Twenty year follow up of three population groups in Serbia: reexamination of University professors in Belgrade. A part of Seven Countries Study. CVD Epidemiological Newsletter 1985;38:119-120.

Nedeljković S, Grujić M, Menotti A, Keys A, Stojanović G, Ostojić M, Kromhout D. Coronary heart disease mortality in three Serbian cohorts - part of Seven Countries Study followed 25 years. Abstracts. Eur Heart J 1989;10:807.

Nedeljković S, Menotti A, Keys A, Ostojić M, Grujić M, Kromhout D, Stojanović G. Coronary heart disease in three cohorts of men in Serbia followed up for 25 years as a part of Seven Countries Study. Kardiologija 1992;13(1-2): 35-44.

Nedeljković S, Ostojić M, Grujić M, Josipović V, Keys A, Menotti A, Seccareccia F, Lanti M, Kromhout D. Coronary heart disease deaths in 25 years. The experience in three Serbian cohorts of the Seven Countries Study. Acta Cardiologica 1993;48(1):11-24.

Kromhout D, Nedeljković SI, Grujić MZ, Ostojić MC, Keys A, Menotti A, Katan MB, Van Oostrom MA, Bloemberg BPM. Changes in major risk factors for cardiovascular diseases during 25 years in the Serbian cohorts of the Seven Countries Study. Int J Epidemiol. Accepted.

Nissinen, Aulikki M. **Professor**

Education

Kuopio Nursery College		1963	Nursery
Helsinki Nursery College		1965	Public health nursery
University of Kuopio	M.D.	1977	Medical doctor
University of Kuopio	Ph.D.	1979	Public health

Professional Experience

Nurse, Kuopio Central Hospital, 1963-1964.
Public health nurse, City of Helsinki, 1965.
Midwife, City of Helsinki, 1966.
Nurse teacher, Helsinki Nursery College, 1970.
Assistant Professor in Public Health, University of Kuopio, 1977-1981.
Professor of Public Health, University of Kuopio, 1981-1982.
Chief of Laboratory of Chronic Diseases, National Public Health Institute, Helsinki, 1983-1985.
Medical Officer, Cardiovascular Diseases Unit, World Health Organization, Geneva,Switzerland, 1986-1988.
Professor in Public Health, University of Kuopio, Medical Faculty, 1988-present.

Special Experience

Co-principal Investigator of the North Karelia Project
Coordinator of WHO global InterHealth-project (Integrated Programme for Prevention and Control of Chronic Diseases).

Committees and Offices

Member of several scientific and administrative boards, Faculty of Medicine, University of Kuopio, 1972-1982, 1988-present.
Expert groups, Ministry of Education and Medical Board of Health, Finland, 1975-1985.
Member, Finnish Academy of Science, Medical Department, 1988-present.
Member, Developing Country Research Council, 1988-present. Chairperson, 1991-present.
Member, Finnish Physical Exercise Scientific Board, Ministry of Education, 1988-1991, Chairperson, 1991-present.
Member, Steering Group for Health by 2000-program, Ministry of Health and Social Welfare, 1988-present.

Selected Publications

Tuomilehto J, Nissinen A, Salonen JT, Kottke TE, Puska P. Community programme for control of hypertension in North Karelia, Finland. Lancet 1980;2:900-904.

Puska P, Iacono JM, Nissinen A, Korhonen HJ, Vartiainen E, Pietinen P, Dougherty R, Leino U, Mutanen M, Moisio S, Huttunen J. Controlled, randomized trial of the effect of dietary fat on blood pressure. Lancet 1983;1/8:1-5.

Puska P, Nissinen A, Tuomilehto J, Salonen JT, Koskela K, McAlister A, Kottke TE, Maccoby N, Farquhar JW. The community-based strategy to prevent coronary heart disease: conclusions from the ten years of the North Karelia Project. Ann Rev Publ Hlth 1985;6:147-193.

Nissinen A, Tuomilehto J, Kottke TE, Puska P. Cost-effectiveness of the North Karelia hypertension program 1972-1977. Medical Care 1986;24(8):767-780.

Pekkanen J, Marti B, Nissinen A, Tuomilehto J, Punsar S, Karvonen MJ. Reduction of premature mortality by high physical activity: A 20-year follow-up of middle-aged Finnish men. Lancet 1987;1473-1477.

Nissinen A, Tuomilehto J, Korhonen H, Piha T, Salonen JT, Puska P. Ten-years results of hypertension care in the community: Follow-up of the North Karelia hypertension control program. Am J Epidemiol 1988;127(3):488-199.

Lammi U-K, Kivelä S-L, Nissinen A, Punsar S, Puska P, Karvonen MJ. Predictors of disability in elderly Finnish men. A longitudinal study. J Clin Epidemiol 1989;42(12):1215-1225.

Nissinen A, Wiklund I, Lahti T, Akkila J, Wilson A, Wahl M, Puska P. Anti-anginal therapy and quality of life. A comparison of the effects of transdermal nitroglycerin and long-acting oral nitrates. J Clin Epidemiol 1991;44(9):989-997.

Pekkanen J, Nissinen A, Punsar S, Karvonen MJ. Short and long-term association of serum cholesterol with mortality. The 25-year follow-up of the Finnish cohorts of the Seven Countries Study. Am J Epidemiol 1992;135(11):1251-1258.

Tuomilehto-Wolf E, Tuomilehto J, Hitman CA, Nissinen A, Stengård J, Pekkanen J, Kivinen P, Kaarsalo E, Karvonen MJ. Genetic susceptibility to non-insulin dependent diabetes mellitus and glucose intolerance are located in HLA region. Br Med J 1993;307:155-159.

Pekkarinen, Maija — Associate Professor

Education

Järvenpää College for teachers of Home Economics		1942	Home economics
University of Helsinki	M.Sc.	1952	Household economics
University of Helsinki	Lic.Agr.Sci.	1958	Nutrition
University of Helsinki	D.Agr.Sci.	1962	Nutrition

Professional Experience

Home economics expert, The Finnish Martha Organization, 1942-1950.
Assistant Professor, Department of Household Economics, University of Helsinki, 1950-1957.
Research work for Doctor's degree, 1958-1961.
Research Assistant and junior fellow, National Research Council for Agriculture and Forestry, Academy of Finland, 1962-1968.
Academic Docent, University of Helsinki, 1966-1968.
Associate Professor, University of Helsinki, 1968-1981.
Acting Professor, Head of Department of Nutrition, University of Helsinki, 1971-1977.

Committees and Offices

Board Member, Foundation for promotion of food production, 1962-1981.
Member, Group of European Nutritionists, 1969-present.
Board Member, National Research Council for Agriculture and Forestry, Academy of Finland, 1971-1976.
Member, Finnish FAO committee and chairperson, Division of Home economics and nutrition, 1974-1982.
Board Member and Vice President, FAO/ECA working party on women and the agricultural family in rural development, 1972-1982.
Chairperson, Research Centre for Home Economics and Consumer Affairs, 1972-1983.
Vice Chairperson, Finnish State Council on Nutrition, 1977-1982.

Honors

Gold Badge of Merit, The Finnish Martha Organization, 1965.
Knight, 1st call, Order of the White Rose of Finland, 1979.
Honorary member:
Finnish Martha Organization, 1977.
Association of Home Economics Teachers, 1979.
Association of Nutrition Therapists, 1981.
Association of University Home Economics, 1983.

Selected Publications

Roine P, Pekkarinen M, Karvonen MJ, Kihlberg J. Diet and cardiovascular disease in Finland. Lancet 1958;2:173-175.

Karvonen MJ, Pekkarinen M, Metsälä P, Rautanen Y. Diet and serum cholesterol of lumberjacks. Br J Nutr 1961;15:157-163.

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Roine P, Pekkarinen M, Karvonen MJ. Dietary studies in connection with epidemiology of heart disease: Results in Finland. Voeding 1964;25:383-393.

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Pekkarinen M, Kivioja S, Jortikka L. A comparison of food intake of rural families estimated by one day recall and precise weighing methods. Voeding 1967;28:470-476.

Pekkarinen M. Methodology in the collection of food consumption data. World Rev Nutr Diet 1970;12:145-171.

Pekkarinen M. Dietary surveys in connection with coronary heart disease studies in Finland. New Trends in Nutrition, Lipid Research and Cardiovascular Diseases. Alan R. Liss Inc. New York, 1981:243-261.

Aho K, Pekkarinen M. Diet and physical activity of men in East and West Finland in 1969. Ann Med 1989;21:241-243.

Puddu, Vittorio **Professor**

Vittorio Puddu was born in 1909 in Ancona, the region of Marche, central Italy, into a family of Sardinian origin.

After graduation in Medicine at the University of Rome he became one of the first Italian doctors who used an electrocardiographic machine, which put him on the track of developing a peculiar interest in the still non-existing discipline of cardiology. He was later trained in this developing discipline in Paris and Vienna, and started what could have been a brilliant university career. However, for a number of reasons he never took a chair, also reflecting his substantially independent personality.

After the Second World War, which took him to Russia as medical officer in the Italian army, he had another term of foreign experience in Paris, and came back with the clear belief that some cardiovascular diseases were of social interest due to their large number and marked severity. Through the financial support of the Ministry of Health he founded the first Centre for Cardiovascular Diseases in Rome, located in the University Hospital of Rome - and then in the St. Camillo Hospital of the same city - but completely independent from the University itself. Initially, the main interest was focused on rheumatic heart disease, which was the prevalent one in those times, while later coronary heart disease became the major interest. In 1956 he founded the first Division of Cardiology in Italy, again at the St. Camillo Hospital and was the chief of that unit until retirement in 1976.

Professor Puddu was a pioneer rich in great intuitions. He established in his country a number of firsts: he was the first to launch epidemiological studies in the medical schools in search of ignored rheumatic and congenital heart diseases, and the first, through the Seven Countries Study, to be involved in epidemiology of coronary heart disease; in his Center and in the Division of Cardiology one of the first cath-labs, the first coronary care unit, and the first cardiac rehabilitation center in Italy were located. A large number of scientific papers resulted from such intense and varied activity.

Moreover, he was a great promoter of cardiology at a national and international level. His fluency in four languages, beyond his native one, put him in the ideal situation for becoming a leader in this action, culminating in his position as Secretary General of the International Society of Cardiology for many years and President of the same society for one term.

Besides all his merits in cardiology Professor Puddu was an eclectic person rich in many hobbies. He was an expert gastronome with official positions in groups and societies in this field; he was a skilled electro-mechanical engineer able to disassemble and fix an ECG machine if needed; he was for some years a renowned champion in outboard motor boat racing and later a valuable competitor in sailboat racing; he was a collector of archeological specimens of small bronze statutes and a constructor of flying airplane models.

His last years were sad and troubled by an aggressive Parkinson disease which took him away in 1991.

Punsar, Sven **Physician**

Education

University of Helsinki, Finland	M.D.	1953	Medicine
Specialist in Internal Medicine		1961	
Specialist in Cardiology		1963	
University of Helsinki, Finland	Ph.D.	1980	Medicine

Professional Experience

Medical Officer, Finnish Army, 1954.
Assistant Physician, Salus Hospital, Helsinki, Finland, 1956.
Research Fellow, Laboratory of Physiological Hygiene, School of Public Health, University of Minnesota, 1957-1958.
Assistant Physician, Helsinki University Hospital, Finland, 1958-1961.
Private Physician, Helsinki, Finland, 1958-1965.
Physician, Student Health Service, 1962.
Assistant Physician (Cardiology), Helsinki University Hospital, 1962-1965.
Assistant Chief Physician, Internal and Pulmonary Medicine, Laakso Hospital, Helsinki, 1965-1985.
Chief Physician, Department of Internal Medicine, Laakso Hospital, Helsinki, 1985-1986.

Special Experience

Project Officer, The East-West studies in Finland, the Seven Countries Study, 1959, 1964-1980.
Consultant, The Mobile Clinic, the National Pension Institute, 1965-1985.
Principal Investigator, The East-West Studies in Finland, the Seven Countries Study, 1980-1984.
Docent in Epidemiology, University of Helsinki, 1981-1986.

Committees and Offices

Member, the Scandinavian Committee on ECG classification, 1966.
Member, Committee for Safety and Efficacy of Drugs, National Board of Health, 1970-1982.
Secretary, Finnish Internists Association, 1971-1973.

Selected Publications

Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies. A classification system. Circulation 1960;21:1160.

The Scandinavian Committee on ECG Classification (Punsar S). The 'Minnesota Code' for ECG classification. Adaptation to CR leads and modification of the code for ECG's recorded during and after exercise. Acta Med Scand 1967;Suppl 481.

Karvonen MJ, Blomqvist G, Kallio V, Orma E, Punsar S, Rautaharju P, Takkunen J, Keys A. Men in rural East and West Finland. Acta Med Scand 1967;Suppl 460:169.

Punsar S, Pyörälä K, Siltanen P. Classification of electrocardiographic S-T segment changes in epidemiological studies of coronary heart disease. Preliminary evaluation of a new, modified classification, with particular reference to the prognostic significance of different types of S-T segment changes. Ann Med Int Fenn 1968;57:53.

Karvonen MJ, Orma E, Punsar S, Kallio V, Arstila M, Luomanmäki K, Takkunen J. Five-year experience in Finland. In: Coronary heart disease in seven countries. Keys A (Ed). Circulation 1970;41(Suppl 1):52.

Punsar S. Cardiovascular mortality and quality of drinking water. An evaluation of the literature from an epidemiological point of view. Work Environment Health 1973;10:107.

Punsar S, Karvonen MJ. Angina pectoris and ECG abnormalities in relation to prognosis of coronary heart disease in population studies in Finland. Adv Cardiol 1973;8:148.

Punsar S, Erämetsä O, Karvonen MJ, Ryhänen A, Hilska P, Vornamo H. Coronary heart disease and drinking water. A search in two Finnish male cohorts for epidemiologic evidence of a water factor. J Chron Dis 1975;28:259.

Punsar S, Karvonen MJ. Physical activity and coronary heart disease in populations from East and West Finland. Adv Cardiol 1976;18:196.

Punsar S, Karvonen MJ. Drinking water quality and sudden death: observations from West and East Finland. Cardiology 1979;64:24.

Räsänen, Leena K. **Associate Professor**

Education

University of Helsinki, Finland	M.Sc.	1970	Nutrition
University of Helsinki, Finland	Lic.Sc.	1977	Nutrition
University of Helsinki, Finland	D.Sc.	1980	Nutrition

Professional Experience

Teaching Assistant, Department of Nutrition, University of Helsinki, Finland, 1970-1971.
Research Associate, National Research Council for Agriculture and Forestry, Academy of Finland, 1972-1977.
Junior Research Fellow, National Research Council for Agriculture and Forestry, Academy of Finland, 1978.
Acting Associate Professor of Public Health Nutrition, Department of Public Health, University of Tampere, Finland, 1979-1982.
Teacher of Nutrition, Faculty of Medicine, University of Helsinki, Finland, 1979-1984.
Senior Scientist, National Research Council for Agriculture and Forestry, Academy of Finland, 1982.
Acting Professor of Nutrition, Department of Nutrition, University of Helsinki, Finland, 1986-1988.
Senior Scientist, National Research Council for Agriculture and Forestry, Academy of Finland, 1989-1990.
Associate Professor of Nutrition, Division of Nutrition, Department of Applied Chemistry and Microbiology, University of Helsinki, 1982-present.

Committees and Offices

Member, Society for Food Science in Finland, 1972-present.
Member, Finnish Association of Public Health and Clinical Nutritionists, 1976-present.
Member, Society of Social Medicine in Finland, 1972- present.
Member of Board, Society of Social Medicine in Finland, 1976-1981.
Member, Nordic Group for Dietary Survey Methodology, 1976-1985.
Member of Council, Federation of European Nutrition Societies, 1979-1989.
Member, Group of European Nutritionists, 1983-present.
Member, Finnish Society for Nutrition Research, 1985-present.
Vice Chairman, Finnish Society for Nutrition Research, 1992-present.

Selected Publications

Räsänen L, Wilska M, Kantero R-L, Näntö V, Ahlström A, Hallman N. Nutrition survey of Finnish rural children. IV. Serum cholesterol values in relation to dietary variables. Am J Clin Nutr 1978;31:1050-1056.

Räsänen L. Nutrition survey of Finnish rural children. VI. Methodological study comparing the 24-hour recall and the dietary history interview. Am J Clin Nutr 1979;32:2050-2057.

Räsänen L, Pietinen P. A short questionnaire method for evaluation of diets. Prev Med 1982;11:669-676.

Moilanen T, Räsänen L, Viikari J, Åkerblom HK, Ahola M, Uhari M, Pasanen M, Nikkari T. Fatty acid composition of serum cholesteryl esters in 3- to 18-year-old Finnish children and its relation to diet. Am J Clin Nutr 1985;42:708-713.

Pietinen P, Hartman AM, Haapa E, Räsänen L, Haapakoski J, Palmgren J, Albanes D, Virtamo J, Huttunen JK. Reproducibility and validity of dietary assessment instruments. I. A self-administered food use questionnaire with a portion size picture booklet. Am J Epidemiol 1988;128:655-666.

Räsänen L, Laitinen S, Stirkkinen R, Kimppa S, Viikari J, Uhari M, Pesonen E, Salo M, Åkerblom HK. Composition of the diet of young Finns in 1986. Ann Med 1991;23:73-80.

Virtanen SM, Räsänen L, Aro A, Ylönen K, Lounamaa R, Tuomilehto J, Åkerblom HK. The 'Childhood Diabetes in Finland' Study Group. Feeding in infancy and the risk of type 1 diabetes mellitus in Finnish children. Diabetic Med 1992;9:815-819.

Räsänen L, Mutanen M, Pekkanen J, Laitinen S, Koski K, Halonen S, Kivinen P, Stengård J, Nissinen A. Dietary intake of 70- to 89-year-old men in eastern and western Finland. J Intern Med 1992;232:305-312.

Moilanen T, Räsänen L, Viikari J, Åkerblom HK. Tracking of serum fatty acid composition: a 6-year follow-up study of Finnish youths. Am J Epidemiol 1992;136:1487-1492.

Lehtimäki R, Moilanen T, Porkka K, Åkerblom HK, Ehnholm C, Rönnemaa T, Räsänen L, Laippala P, Viikari J. Association of serum lipids with apolipoprotein E phenotype and linoleic acid content of serum cholesteryl esters in the Cardiovascular Risk in Young Finns Study. Nutr Metab Cardiovasc Dis 1993;3:61-65.

Taylor, Henry L.

Professor
Born February 2, 1912
Died November 10, 1983

Education

Harvard College, Boston, MA	B.A.	1935	Biochemistry
University of Minnesota, Minneapolis, MN	Ph.D.	1941	Physiology

Professional Experience
Assistant Professor, Physiological Hygiene, University of Minnesota, 1944-1949.
Associate Professor, Physiological Hygiene, University of Minnesota, 1949-1956.
Professor, Physiological Hygiene, University of Minnesota, 1958-1983

Special Experience
Investigator, Aging, personal characteristics, and coronary heart disease in Minnesota businessmen, 1948-1983.
Principal Investigator, Epidemiology of coronary heart disease in US railroad employees, 1956-1972.
Fieldwork epidemiology of coronary heart disease among employees of Italian National Railroads, Rome, Italy, 1962 and 1967.
Director, Cooperative study of the prevalence of hyperlipoproteinemias for the Minnesota Unit of the Lipid Research Clinics, 1972-1982
Co-investigator, Minnesota Clinic of the Multiple Risk Factor Intervention Trial, 1973-1982

Committees and Offices
Research Committee, American Heart Association, 1960-1965.
Executive Committee, Council on Epidemiology, American Heart Association,1964-1965.
White House Conference on Food, Nutrition and Health; Consultant to Panel on Adults in an Affluent Society: The Degenerative Diseases of Middle Age, 1968.
Chairman, Steering Committee of the Cooperative Study on the Feasibility of Physical Activity in Trials of Coronary Heart Disease Prevention, 1966-1969.
Member, Panel on Exercise, National Heart and Lung Institute, Task Force on Arteriosclerosis, 1971.
Member Division of Research Grants, National Institutes of Health Study Section, Applied Physiology and Bioengineering, 1972-1976.

Selected Publications

Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation. University of Minnesota Press, Minneapolis, MN, 1950;Vol 1-2:1-1385.

Taylor HL, Keys A. Adaptation to caloric restriction. Science 1950;112:215-218.

Taylor HL, Buskirk ER, Henschel A. Maximal oxygen intake as an objective measure of cardio-respiratory performance. J Appl Physiol 1955;8:73-80.

Taylor HL, Klepetar E, Keys A, Parlin W, Blackburn H, Puchner T. Death rates among physically active and sedentary employees of the railroad industry. Am J Publ Hlth 1962;52:1697-1707.

Keys A, Taylor HL, Blackburn H, Brozek J, Anderson JT, Simonson E. Coronary heart disease among Minnesota business and professional men followed fifteen years. Circulation 1963;28:381-395.

Taylor HL, Blackburn H, Brozek J, Parlin RW, Puchner T, Monti M, Puddu V, Menotti A, Keys A. Railroad employees in the US and railroad employees in Rome. In: Epidemiological studies related to coronary heart disease: Characteristics of men aged 40-59 in seven countries. Keys A, *et al* (Eds). Acta Med Scand 1967;460(Suppl 180):55-115.

Taylor HL, Blackburn H, Keys A, Parlin RW, Vasquez C, Puchner T. Five year follow-up of employees of selected US Railroad companies. In: Coronary heart disease in seven countries. Keys A (Ed). Circulation 1970;41(Suppl 1):20-39.

Taylor HL, Buskirk ER, Remington R. Exercise in controlled trials of the prevention of coronary heart disease. Fed Proc 1973;32:1623-1627.

Taylor HL, Jacobs DR, Schucker B, Knudsen J, Leon AS, DeBacker G. Questionnaire for the assessment of leisure time physical activities. J *Chron Dis* 1978;31:741-755.

Taylor HL. Physical activity: Is it still a risk factor. Prev Med 1983;12:20-24.

Toshima, Hironori **Professor/Director**

Education

Kyushu University, Faculty of Medicine	M.D.	1952	Medicine

Professional Experience

Internship, Kyushu University Hospital, 1952-1953.
Residency, the 1st Department of Medicine, Kyushu University Hospital, 1953-1958.
Research Fellow, Laboratory of Physiological Hygiene, University of Minnesota, USA, 1963-1964.
Associate Professor, the 3rd Department of Medicine, Kurume University School of Medicine, 1959-1977.
Professor, the 3rd Department of Medicine, Kurume University School of Medicine, 1977-present.
Director, The Institute of Cardiovascular Diseases, Kurume University, 1977-present.

Committees and Offices

Director, Japanese Circulation Society, 1979-present.
Chairman, Idiopathic Cardiomyopathy Research Committee, Ministry of Health and Welfare of Japan, 1980-1986.
President, the 54th Annual Scientific Meeting of the Japanese Circulation Society, 1990.
Member, Scientific Council on the Rehabilitation of Cardiac Patients, International Society and Federation of Cardiology, 1981-1988.
Member, Board of Directors, Japanese Heart Foundation, 1990-present.
President, the 12th Scientific Session of the Japanese Society of Clinical Nutrition. 1990.
President, the 26th Scientific Session of the Japanese Association for Cerebro-cardiovascular Disease Control, 1991.
Chairman, Prevention Committee, Asian-Pacific Society of Cardiology, 1991-present.
Chief Director, Kimura Memorial Heart Foundation, 1992-present.
Chief Director, the Japanese Association for Cerebro-cardiovascular Disease Control, 1991-present.

Selected Publications

Cueto J, Toshima H, Tuna N, Armigo G, Lillehei CW. Vectorcardiographic studies in acquired valvular disease with reference to the diagnosis of right ventricular hypertrophy. Circulation 1966;33:588.

Simonson E, Tuna N, Okamoto N, Toshima H. Diagnostic accuracy of the vectorcardiogram and electrocardiogram. Am J Cardiol 1966;17:829.

Toshima H, Cueto J, Lillehei CW. Vectorcardiographic studies in acquired valvular disease with reference to the diagnosis of left ventricular hypertrophy. Circulation 1967;35:132.

Toshima H, Fukami T. Clinical features of idopathic hypertrophic cardiomyopathy. Jpn Circ J 1971;35:777.

Toshima H. Prognosis of patients with rheumatic heart disease and some aspects in its prevention. Jpn J Med 1974;13:95.

Toshima H, Koga Y, Uemura S, Jinnouchi J, Kimura N, Nakakura S. Echocardiographic study on hypertrophic cardiomyopathy. Jpn Heart J 1976;17:275.

Toshima H, Koga Y, Yoshika H, Akiyoshi T, Kimura N. Echocardiographic classification on hypertensive heart disease. A correlative study with clinical features. Jpn Heart J 1976;16:377.

Toshima H, Tashiro H, Sumie M, Koga Y, Kimura N. Changes in risk factors and cardiovascular mortality and morbidity within Tanushimaru 1958-1982. In: Nutritional prevention of cardiovascular disease. Lovenberg E, Yamori Y (Eds). Academic Press, Orlando. 1984:203-210.

Toshima H. State of the art in patient education in Japan. In: The education of the patient with cardiac disease in the twenty-first century. Wenger NK (Ed). Le Jacq Publishing Inc, 1986:292.

Nishi H, Kimura A, Harada H, Toshima H, Sasazuki T. Novel missense mutation in cardiac β myosin heavy chain gene found in a Japanese patient with hypertrophic cardiomyopathy. Biochem Biophys Res Commun 1992;188(1):379-387.

This highly readable monograph, composed and edited by the investigators, is an unusual history of an unusual undertaking, The Seven Countries Study, a landmark in cardiovascular disease epidemiology. It is doubtful that any other major long-term scientific enterprise, this one in its 35th year, has been more appealingly documented by the scientists and clinicians involved.

The introduction is by the founder of the Study, Ancel Keys, about how it began, with the ideas of collaborators looking beyond their clinics and laboratories to broader questions about the origins of heart disease. The other investigators provide delightful, personalized details of the study's tribulations in the field, about its contributions to survey and follow-up methodology in epidemiology, and about its findings. An overview is given of results of the Study, along with commentary by Frederick Epstein, long-term observer of the scene, on the public health influence of the Study.

The Seven Countries Study was the first to carry out both cross-sectional and longitudinal cohort studies in populations purportedly contrasting in cardiovascular disease rates and in lifestyle, including diet. It was the first to apply regressions developed in one population to men of similar age in another, demonstrating the universality of CVD risk factors but their different *force* in individuals and contrasting cultures.

Relatively short and easily read, the volume contains the essence of the design, operation, main results, and public health import, and much more of the flavor, of this pioneering study in cardiovascular disease.