

ON THE TRAIL OF HEART ATTACKS IN SEVEN COUNTRIES

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The Seven Countries Study was the first to examine systematically the relation among lifestyle, diet, and the rates of heart attack and stroke in contrasting populations. It has been one of the finer scientific adventures of our time and of the field of cardiovascular disease epidemiology. The idea of the study arose in various forms in the minds of imaginative individuals capable of integrating clinical, laboratory, and population evidence. Ancel Keys, the leader of the study, gave the concept its broad scope as well as its substance and direction.



This, my personal account of adventures in the field, conveys only a tiny part of the excitement, and recalls only a few of the many contributions and difficulties of the undertaking. Keys and I, and others, have addressed these issues elsewhere. Evaluation of the scientific and public health import of the Seven Countries Study is better left to others.

In the late '50s, when this project was conceived and mounted, there was no “big science,” and nothing like a Program Project. So there was neither precedent nor support for a properly organized, rigorous, centrally directed, adequately funded, multi-center undertaking. But never mind. The Seven Countries Study was bold and forward-looking for its day, a pioneering effort. Its results, elucidating the lifestyles and mass phenomena that determine high and low population rates of heart attacks, have affected all our lives, and have powerfully influenced the public health.

These field experiences are presented with little balance among geographic settings, survey periods, or contributions made. In fact, no coordinator was present at all surveys in all areas, though Alessandro Menotti and I, between us, came close. This represents only a fragment of the adventure and is long on anecdote and short on concept, method, and results.



Admittedly, such a presentation says little for the long and fascinating history of science. On the other hand, many would find it interesting, I suspect, to read such personal accounts of the peregrinations, emotions, breakdowns, and triumphs of those engaged in some of the grander research projects, say, the Manhattan Project, or the Polio Vaccine Trials. Mainly for this reason, I persist.

The scientific literature today bears the fruits of Seven Countries Study researches. My purpose here is to provide the flavor — an account of the joys and tribulations of our field surveys in rural areas around the world. There traditions of subsistence living went on much as they had for centuries. I also try to depict the character of these lands and these peoples that the investigators have studied for more than thirty years.

You are welcome to share our adventures in the field.

Overview: The Seven Countries Study in Brief

Ansel Keys at Minnesota, and his colleagues in seven countries, posed the hypothesis that differences among populations in the frequency of heart attacks and stroke would occur in some orderly relation to physical characteristics and lifestyle, particularly composition of the diet, and especially fats in the diet.

To test this idea we carried out surveys from 1958 to 1970 in populations of men aged 40-59, in eighteen areas of seven countries, with follow-up for deaths in the cohorts up to the present day. The formal surveys were undertaken after successful pilot experiences in Finland, Italy, and Greece in 1956 and 1957. Most of the areas were stable and rural and had wide contrasts in habitual diet. In those days, we did not consider involving women because of the great rarity of cardiac events among them, and the invasiveness of our field examinations.

The Seven Countries Study is the prototypical comparison study of populations, made across a wide range of diet, risk, and disease experience. It was the first to explore associations among diet, risk, and disease in contrasting populations (ecologic correlations). Central chemical analysis of foods consumed among randomly selected families in each area, plus diet-recall measures in all the men, allowed an effective test of the dietary hypothesis. The study was unique for its time, in standardization of measurements of diet, risk factors, and disease; training its survey teams; and central, blindfold coding and analysis of data.

There were, of course, limitations: the relatively small number of units for ecological correlations; the selection of the samples in the different geographic areas in part for reasons of convenience; and the technical challenges of conducting surveys across cultures by national teams, often working under difficult field conditions.

The core of investigators was recruited by Ansel Keys and the study coordinated from the Laboratory of Physiological Hygiene, located in offices under Memorial Stadium, Gate 27, at the University of Minnesota. I served as Project Officer in the early years, while Henry Taylor directed the Railroad Study, the U.S. component of the Seven Countries Study. A few years into the study, central coordination of data was shifted to Alessandro Menotti at the University of Rome. All field studies were carried out under the aegis of a National Heart Institute grant. Local support was always substantial, however, in that the central grant only averaged about \$25,000 a year per collaborating center. Both public and private sources, as well as the World Health Organization, provided direct and logistic support.

The study has been criticized for the method in which populations were selected for the study, and the way that the population (ecologic) correlations, with limited numbers of units, were carried out. These days, the configuration of populations for such internal and international comparisons is strengthened by the random selection of greater numbers of units. But the Seven Countries Study was state-of-the-art for its time, and the concept ahead of its time. Ecologic correlations are relatively weak in arriving at causal inference about disease. However, they are crucial indicators of population causes of disease, and of public health preventive strategies, where the epidemiologic evidence is congruent with that from the laboratory and the clinic.

The Seven Countries Study, more than any other cardiovascular disease study, has directed attention to the causes of population rates of disease, while confirming the importance of an individual's risk within populations. It documented major differences in the mass phenomena related to differences in disease rates, and it demonstrated the degree to which composition of the diet — particularly levels of saturated fatty acids and mean serum cholesterol levels — predict present and future population rates of coronary heart disease.

The predictive equations derived from the population correlations provide the general rule, while departure from prediction points up important exceptions, such as the excess of coronary heart disease in East Finland and its rarity in Crete. These exceptions, in turn, have provided impetus to further research into causal factors other than dietary saturated fatty acids and cholesterol.

Collaborators

Ansel Keys, Principal Investigator

The concept of the Seven Countries Study arose independently in the minds of innovative physicians and investigators, who were interested in heart diseases beyond the clinic, and at the same time, were capable of synthesizing evidence from clinic, laboratory, and the population. Keys gave the concept its bold design, and provided the critical vision and leadership to bring about the study.

The background of the study lies in Keys's application of physiological principles and knowledge to health, in a quantitative human biology that he called physiological hygiene. The wartime observations and experiments of Keys and colleagues at Minnesota profoundly changed their thinking about the modifiability, by exercise, calorie restriction, and bed rest, of such presumably immutable attributes as body build and type, circulatory responses, and blood pressure and cholesterol levels. Moreover, Keys was facile with computation, including regression equations, which extended the groups' thinking to correlations among individual levels, and then among population levels, of risk attributes, behavior, and disease rates.

Keys states quite simply that in casting about for major researchable issues in biology and disease at the end of World War II, he was particularly impressed with news reports of the epidemic of heart attacks among executives. He promptly set about to study the characteristics of executives in health with the intent to follow them for the risk of later disease. Inadequate in numbers and ranges of variables, the Minnesota Business and Professional Men's Study became, nevertheless, the pioneer longitudinal epidemiological study of cardiovascular disease.

But it was Keys's Sabbatical year at Oxford, and related travels in 1951-1952, that opened his eyes to cultural differences in diet, behavior, and disease risk, and put him in touch with nutritional and clinical scientists beginning to consider such differences. The contrasts they found in risk by social class in Italy, Spain, South Africa, and Japan, set off Keys' imagination and led to his conceptual formulations of the relation of mass cultural phenomena to the major diseases and their risk. Thus, Keys' rich preparation and experience led him and his colleagues to a broad view of human biology and health. This was combined with his quick intelligence, clear thinking and writing, and a focused, prodigious energy. All Keys's background and skills were brought to bear on the Seven Countries Study.

At the same moment in history, opportunities for research grew rapidly with expansion of the review and support role of the National Institutes of Health, and of the new National Heart Institute. At this time, Keys's match-up with great clinicians completed the picture – such leaders as Paul Dudley White of Boston, Vittorio Puddu of Rome, Noboru Kimura of Japan, John Brock of Capetown, Martti Karvonen of Helsinki, and Christ Aravanis of Athens. All saw beyond the clinic and beyond the individual patient – to the origins of common diseases – in the population and in society.

Keys' leadership was also crucial to the effective formulation of ideas into grant proposals, and over the

years of the study, to synthesis and preparation of the study's major monographs. All these attributes and practices were in the best 'Old School' tradition. Nowadays, academic practice, at least in epidemiology, is perhaps more conducive to true collaboration, with greater sharing of ideas, responsibilities, publications, and credits. But, just as in the families of old, the patriarch of the Seven Countries Study, Ancel Keys, provided priceless experience, superb careers, and a model of excellence for his fortunate colleagues.

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The Seven Countries Study: Yugoslavia

Why Yugoslavia?

The questions that Keys and his colleagues addressed in Yugoslavia were based on preliminary evidence developed by Ratko Buzina and his local associates in the early 1950s. They had found remarkable differences in dietary fat intake and in serum cholesterol levels between the meridional region of Dalmatia and the eastern plains of Slavonia in Croatia. Another diet contrast tested in Yugoslavia was the effect of predominantly animal fats in the east versus vegetable fats in the west.

Ratko Buzina met Ancel Keys through Joseph Brozek, who was on Sabbatical in Zagreb from the University of Minnesota. Buzina later spent 1956 in the Laboratory of Physiological Hygiene, studying dietary fat effects on blood coagulation.

During that year, he and Keys laid plans for the survey in Croatia. Later, the formal proposal for the Croatian part of the Seven Countries Study was written by Keys and Buzina in one day, as they sat on a bench in a lovely Roman park in the springtime.

Pilot experience in Yugoslavia also had revealed that farmers and fishermen in Dalmatia and farmers in

Slavonia responded to surveys in consistently high numbers. In fact, the eventual survey response rate in Dalmatia was 98 percent, and in Slavonia, 95 percent. Parallel clinical and dietary surveys were first carried out in those areas in September and October of 1958 by an international team.

Dalmatia, First Round, 1958

The following personal accounts are taken mainly from journals I kept during the critical starting period for the Seven Countries Study surveys in Yugoslavia in 1958.

September 23 : Arrival

I arrived today in Yugoslavia by train from Munich, declaring our survey medical equipment at the Austrian border where there was only a cursory customs inspection. Our international team has assembled rapidly in Zagreb. As we explore the city, it shows evidence of former Austro Hungarian elegance, but in Tito's Yugoslavia of today, it is poor and somber; only an occasional automobile is seen in the streets. Zagreb maintains, nevertheless, two symphony orchestras, a lively Ritz Bar and Esplanade Hotel, and a brand-new, high-rise building in mid-town. All this is amidst a profound urban depression, seemingly both economic and spiritual.



On our first evening in Zagreb – a Saturday – Buzina took Austin Heady, of London, and me to the local press club. It was decorated in dull brown, with food to match. According to Buzina, the jukebox and TV have ruined the traditional ambiance of the club. As we left the building, we encountered dances in halls all along the main street – people milling about drunkenly, in an eerie atmosphere of sad abandon.

The men in Zagreb run the gamut of physical stereotypes, from swarthy, mustachioed Montenegrins to wiry Serbian peasants to stately Croatian aristocrats. The women are equally varied, and some are striking, despite their attempts at East-Bloc haute couture.

September 26

This morning, before leaving for Split and the Dalmatian coast, a small group from our team went for a stroll above town to the villa of the wartime governor, a Nazi sympathizer. The villa is now a handsome inn and restaurant with a view over the foggy valley and its autumnal woods, the city in the far distance.

Later, after a rickety train trip out to the coast at Split, we narrowly missed a ferry to our destination, Makarska, and so spent a sunny afternoon touring Diocletian's Palace, the grounds of which embrace two thirds of the town. A hundred-year renovation plan for the palace is underway.

The ferry trip down the coast was delightful, but we were exhausted by the time we checked in at Hotel Jadran, our central headquarters in Dalmatia. All slept soundly in preparation for the first day and formal

opening of the Seven Countries Study.

September 27

Makarska is a small port on the meridional edge of a severe plateau of gray, crystalline limestone abutting the Adriatic and extending deep into the interior of Bosnia-Herzegovina. The seaward slopes are terraced in vineyards and ancient oliviers. This morning, shepherds huddle in the dawn, housewives scurry toward the village pumps, and farmers move into the olive groves, all preoccupied with survival in a land where water and soil are scarce. In contrast to the rudeness of the land, the sea is calm and magnificent. Through a soft haze, the Adriatic archipelago is barely visible, mysterious, on the horizon.

Our first days in the Hotel Jadran are occupied with training and celebrations with colleagues, spouses and international 'parachutists' into this auspicious opening of the Seven Countries Study. Intensive planning meetings and discussions go on through the day, and in the evenings, long and formal dinners. Once these opening ceremonies are completed, we trust the dignitaries and hangers-on will depart, leaving the working survey team to its task.

September 28 : Survey Day 1

We all rose early this morning to say good-bye to Paul Dudley White. This popular and distinguished Boston cardiologist – physician to presidents – shows little evidence of aging, in gait or mentality. He is always charming, a bit garrulous, and perpetually curious.

His concepts about the prevention of heart attacks are as simple as they are powerful. For example: 'A heart attack after age eighty is the work of God; before age eighty, a medical failure.'

In the first survey village, of Tucepi, just south of Makarska, there was a five-minute power failure today that required a call to the central power station which promised no further breaks (eventually proving a false promise). Our technicians are largely inexperienced, but they are industrious and eager to learn.

The clinicians, in contrast, are well trained, familiar with American nomenclature and literature, and make thorough examinations while remaining largely on schedule. The electrocardiographic room is the usual survey bottleneck, but today we were on track. Only two men were excluded from the exercise test, one due to emphysema and the other for hip disease.

Dalmatia

October 1 : First Night Out

Early in our first survey week in Dalmatia, we were invited to the home of a local fisherman living a short way down the coast from our headquarters hotel. As we left the hotel, our co-leader and 'den mother,' Anna Brodaric, impressed upon us the necessity to be on our 'best behavior,' whatever that might be, while in the fisherman's household.

After the initial embarrassed exchanges on each side, the ice dissolved quickly in the glow of the lanterns in the simple dwelling, abetted by an equivalent internal glow from the prosceka, a heavy, sweet, native wine.

The fisherman's dark-eyed wife and daughters served platters of baby octopus and squid and pink lamb. I smiled and passed the first plate of squid to my table partner without serving myself. Abruptly, I felt a sharp kick in the shins from across the table. Only when I called the platter back and served myself generously did Anna's imperious glare relent.

For the rest of the evening, this gustatorily unadventurous, gastro-intestinally fragile, American doctor was not allowed to decline any of the things he knew could render him wretchedly ill, even nonfunctional. There would be no greater insult to a fisherman's family than refusing offers of food, particularly the best seafood that could be scavenged along this scrawny, over-fished coast.

After a rollicking evening that got the team off on a strong footing with the locals, our hosts urged us to hurry onto the beach to watch the village fishing boats come in. It was a Biblical sight! A large semi-circle of boats, at first twinkling far out at sea, merged rapidly in the cove. The curved prows of the lead net boats drove fast ashore, grinding to a halt on the pebbly beach, their carbide lamps ablaze, sputtering, and swinging wildly.

From the dark behind us emerged dozens of local fishermen to seize the shrouds and close the circled nets. The boats, lights, and toiling men, and the nets teeming with sardines flashing brilliantly, made a stunning scene of classic and simple beauty. This harmonious activity had surely been repeated over untold centuries on that coast. The labors we observed this night must have been similar, in fact, to those of Christ's companions on Galilee, 2,000 years ago!

Then, with 'dobra noches' all around, kisses on the cheeks and hugs from our hosts, we tore ourselves away from that captivating place and marched up the coast along the beach in high spirits. Halfway to the hotel, our merry crew was surprised on encountering an amazing wind, the first of many we were to experience in the next weeks. The Bura, a form of sirocco, is sucked from the mountains, through the ravines, across the beaches, and out to sea, by a huge vacuum sitting over the waters. It brings with it everything not tied down. We continued to struggle up the beach, leaning against the wind in a way I had experienced only in my youth in Florida during pre-hurricane sorties.

With increasing excitement from the gale, much squeezing of linked arms, shouts, and flashing smiles, we made our way down the two miles of beach to our hotel. The melancholic husband of one technician, out on the left flank of our chain, stumbled along with a bottle of proscoka cradled in his arms, muttering in broken English, 'Happiness – cheap – from a bottle!'

We arose the next morning to the stunning sight of the Bura sweeping the seas strangely away from the coast in huge curled sheets, like sails. I realized that my new bathing trunks and beach towel were no longer hanging on the balcony railing and were probably many miles out to sea. We girded for a return to the field work. In the week that followed our outing to the fisherman's cottage, all remained healthy and happy.

October 3rd

Back in the field today, we get terrible electrocardiograms using homemade, brine-soaked pledgets, because we have not yet received our equipment with its precious Sanborn electrode paste.

The technicians still work slowly, and AC interference makes their work yet slower, so that we average a complete electrocardiogram only every twenty minutes. Our frustration is assuaged only slightly by the magnificent view from the site of the survey station in Podgora, the Civic Center, perched high above the sea. Moreover, people bring us 'moste' daily, the early stages of the local wine, along with fresh figs,

grapes, and apples by the basketful. Constipation will be no hazard in this land!

Of all the man-made and natural hazards we've so far encountered, the greatest has been the frequent Bura howling from the mountains and creating noise and confusion so great that we must close field operations until it blows itself out. Everything not fastened down is whipped out to sea: serum samples hung to dry, dish towels, and, as recounted earlier, new bathing suits.

But just as we could not predict all the hazards of the field, neither could we have imagined all the delights: the warm collegiality, visits to the homes of farmers and fishermen, strolls in the hills among the ancient oliviers, friendly donkeys and goats, and the soft, scintillating moonlit nights above the sea. We listen, fascinated, to the heroic tales of Tito's partisans, and of a survivor of Auschwitz. Our local faculty and staff harbor the yearnings of all people battered by years of war and terror, who seek emotional release and intellectual liberty. It is amazing how they have kept their humanity intact.

October 10

Our backs and livers take a tremendous jarring every day on the narrow, winding, rocky road when we have to drive the coast to new villages. The road is quite dangerous. One wheel off the side, or an unexpected encounter with a 'Dalmatian Jeep' (a donkey), would send our Jeep bounding from terrace to terrace down to the sea!

We're often irritable in the mornings, possibly due to an inadequate breakfast, growling bowels from the previous night's wine and garlic, and burning tongues from scalding, lemon-water tea and local cigarettes. When not required to breakfast on anchovy sandwiches and slivovica (plum brandy) with local officials, we have a soft roll and honey at the hotel, always avoiding the unpasteurized butter.

We are 300 electrocardiograms behind schedule in mounting with a Hungarian stapler. My thumb is bruised and bleeding from operating this 'gawd-awful' machine. In an emergency, we use Scotch tape to affix the strips onto cardboard mounts, and Keys suggests that we send a cable to 3M's Chairman McKnight, himself, reading: 'Stuck for sticky stuff. Send one mile of 3/4 inch Scotch tape.' (Fortunately, we didn't carry out this suggestion, since we found that all electrocardiograms tacked down with Scotch tape quickly became blackened permanently under the tape.)

October 12 : Another Sunday Free

On a rare whole day off, a small group of the survey team put to sea for a fishing expedition. It included Brozek, his son Peter, Zetterqvist, Dujan Jurela, the local doctor, and three local fishermen. Our leader was a former chief partisan of this coast, a handsome brute of a man who gave the impression of loving life, wine, women, and fighting in wars. We lay about a kilometer of line with more than 500 lead-weighted hooks baited with chunks of sardines.

The morning was warm, a soft haze hovering over the flat calm of the sea. The peaks of the coast to the east were eerily grandiose in the contra jour light; plane after plane of dark mountain ranges rose from the mist, while the island of Hvar loomed mysteriously in the west. We pulled onto a small island where one of the fishermen cooked breakfast over coals: fresh sardines and small tuna. Idly and unsuccessfully, I cast



spinning gear with a slice of squid for bait.

After consuming more than usual of the breakfast fish, I discovered live ascarids just under the skin, and abruptly stopped eating. I suppose all the fish were infested, but it was a shock to find the round worms still wriggling. The fishermen were obviously scornful of my poor appetite and inability to drink slivovica so early in the morning. They wondered also at the elaborate protections I take against sunburn due to my fair skin, and they wholly disdained my light spinning gear for fishing. Soft Americans have many strikes against them when attempting to socialize with tough local peasants!

On the return voyage, we spent three hours droning about in the hot mid-day calm, searching for the white gourd buoys we had left to mark and hold up the fishing lines. My binoculars usually picked them up first. Hauling in the lines was a rhythmic process of age-old tradition; synchronized bronze arms coiled the lines neatly back into straw baskets. We could see magnified the whitish outlines of the raja (stingrays) on the lines as they spiraled up from the depths, like runaway kites. Sixteen rays were landed, from one to four feet in diameter, with only a meager catch of other shark-like and smaller fishes. To our disappointment, Brozek, the only Slavic-speaking team member, tended not to translate the fishermen's conversations, which were apparently mostly about wartime experiences and the poor state of coastal fishing.

At the hotel that evening, one ray was filleted and served roasted. I felt queasy from the day's fare of slivovica, fatty bologna, pickles, wine, and worm-infested tuna, and couldn't enjoy the ray. The meat, however, was white and of pleasant consistency.

October 13

Finally, our daily survey routine is 'perfected.' During the last days, we have worked in a Swedish-built summer camp located on the coast. The gasoline generator functions splendidly, and there is no hitch in the schedule, now running at forty men a day. This is largely due to uncomplicated electrocardiographic tracings and a stable power source.

The recent Bura has torn an estimated one-third of the olive crop from the trees. Strangely, there is no effort to recover the fallen olives for immediate pressing.

This morning we passed in the street a magnificent gypsy patriarch wearing a grand black mustache and surrounded by vary-colored straw baskets. He objected to having his picture taken and I didn't push the issue.

October 14

Today was survey 'moving day,' pushing ever farther south on the good ship Budva with a cold following wind and occasional bursts of sun. The little craft is remarkably stable and speedy and has great facility at docking.

As we sailed past, we bade goodbye to our 'completed' villages, Tucepi, Podgora, Igrani, and Zivogosce. Thereafter, nearing Bosnia, we encountered only 'virgin,' unsurveyed coastline, and smaller, poorer towns. Entering the bay made by the long peninsula of Peljesac, we passed the wild southern-most tip of Hvar and headed directly to our next village, Gradac. On board, our Zagreb doctors clowned a great deal for the benefit of the female staff, and I took photos galore of our happy-go-lucky group. On the voyage down the coast the Budva played hide-and-seek with the Brozek's car proceeding south on the coastal road. Our boat's captain joined in the fun, sending piercing blasts of the ship's horn echoing from the rocky massif

whenever we sighted the car. When we docked briefly in each community, much concern was voiced that our boat had been signaling distress.

October 16

We are now into the 'dog days' of the grinding, oppressive survey routine. The team's favorite way to relax in the evening seems now to center around the prozecka, the local equivalent of a cream sherry. We add to this the music from phonograph records and Brozek's guitar and endless Slavic folk songs. My three albums, played on a wretched portable player rented locally, are beginning to pale: one of Odetta ('I've Got the Whole World in my Hand'); one by Tutti's Trumpets, a big swing band; and the last a Kid Ory New Orleans style record.

We had a long electrocardiographic mounting session this evening with much pleasant banter (and less pleasant singing) with the From-Hansen couple, team visitors from Denmark, working quietly and diligently. He sings bass and staples records with great aptitude. We almost have 'cardiac arrest' each time the stapling machine jams, fearing that it will never function again. One technician writes names and numbers on the records, and Peter and Margaret Brozek arrange cards for mounting the resting and post-exercise records. From-Hansen cuts the strips with diligence and accuracy. Lilianna and I make a good team arranging and Scotch-taping the records prior to stapling, and it looks as if we will get the whole batch from Dalmatia mounted by the end of the week.

October 18

Last night, we celebrated with many warm toasts to the approaching mid survey break, a full week between Dalmatia and Slavonia. Buzina made certain that I did not draft all toasters to mount electrocardiograms after dinner. Rather, we danced and sang and went to bed after 1 a.m., waking before 5 a.m. for the bumpy bus ride up the coast to Split, and then by train to Zagreb.

Hazards in the field

We are told that the Dalmatian coastal road from Split south to Dubrovnik was last redesigned and repaired under Napoleon Bonaparte! A couple of men in every village along the route work full time to maintain the road, filling potholes in the clay, scraping and smoothing and tamping. There is much leaning on shovels, because the work is hard and hot.

We have learned that we can transport our survey team from coastal village to village more effectively and comfortably by boat than by bus or jeep. Ferry service along the coast is reliable and on a reasonable schedule, and the small ships tie up directly to the wharf of our headquarters hotel, the Jadran. We trundle generator and electrocardiograph machines and laboratory equipment aboard ship and accompany them to the next stop, spending one to three days surveying each community.

Power variations are continuous and power failures common, several times a day. So we use regulators and on many days, we keep the U.S. Army surplus gasoline generator running all day, placed as far from the examination site as possible to reduce noise.

Wasps were an unanticipated hazard in the field in one village. Our faithful Jeep driver, with a long cane pole and a gasoline-soaked flare, smoked out their nests under the eaves to reduce the risk of stings among staff and participants.

One field hazard required particular ingenuity. After the blood sample is centrifuged, the serum, separated in standard 0.1 milliliter aliquots, is pipetted in four spots onto Watzman number 2 filter paper and hung to dry. We had not anticipated that specks deposited by flies landing on the paper would contain cholesterol! Occasionally, we were forced to hire a local child to fan the drying serum samples to fend off the flies. The dried strips are then cut, two kept in the local laboratory and two placed in separate glycine or wax paper envelopes and sent air mail for analysis at the University of Minnesota.

The Dalmatian Diet

The faculty met for a short seminar tonight (October 8) on nutrition in Dalmatia. Edwin Ferber, Director of Nutrition at the Central Institute of Hygiene in Zagreb, described a high intake of grains from breads, with a recent shift from corn to wheat flour. He claims that the best local products, those of greatest nutritional value, are sold through traveling tradesmen to urban markets. Wives sell eggs because egg money is traditionally theirs, although children are known to steal eggs from under the chickens for money to buy sweets.

Milk products are available in the area, with most of the milk skimmed and fed to hogs. Local children drink about 350 ml. of whole milk daily. Ferber suspects endemic glycine deficiency from the predominantly vegetable protein diet. Vitamin A intake is very low, as is fat intake overall, a usual association. Keys commented that the U.S. National Research Council's allowances for Vitamin D and calcium are probably higher than required.

Rickets is widespread in Dalmatia but is apparently worse in Bosnia and Serbia. The nearby Moslems, who it is said must pay as much as 300,000 dinars dowry for a wife (\$10,000), apparently choose nutritional deficiency over wife deficiency!

Most of the ten percent fat in the coastal diet comes from lard; the locals never use butter. Ferber maintains that we must do seasonal surveys here because of the remarkable seasonal variation in foods available.

For the diet survey, Fidanza and Ferber grind up aliquots of meals collected in randomly selected households and put all under alcohol, then in the deep freeze for later tests of total lipids, fatty acids, amino acids, and nitrogen. Fidanza has been persistent in shopping around local markets to find such locally exotic items as spinach, sheep's milk, and turnips, which others said would be impossible for him to buy.

Slavonia, First Round, 1958

October 28

The Slavonian region of Croatia is characterized by drab villages without centers, strung one-house deep along a two- to three-kilometer main street of pitted, slippery clay. These villages are surrounded by vast rich plains extending far into the Levantine mists. Monstrous black pigs snuffle along the roads, scattering before our jeep, grunting in dirty belches. The cattle herds are immense. Myriad fat geese surround us.



In fact, there is every evidence of great material richness here, but, as we learn, equally great spiritual poverty. The homes are unkempt, the water filthy. Hygiene is wretched; the folk obese and sodden, living under a constant downpour of rain (and slivovica). Stalin's genocide did not reach this far and the wealthy farmer, Kulak class persists here, with ingrained prejudice against orders of any sort, government of all sorts, and our taking their blood, in particular. We are told that the farmers here resent being 'guinea pigs.' A rumor going around says that once our dietary survey indicates their 'high' eating standards, their taxes will be increased. For these and other reasons, we have had a poor start in the town of Dalj. I wonder if this suspicious peasant independence may be exaggerated a bit by our urbane, upper class Zagreb colleagues.

October 29

Today in Dalj we broke our backs examining forty-three participants. None was drunk, and the sun was shining. The electrocardiograph machine that I recently carried all the way to Paris for repairs is still unstable, but seems to be improving. We sense, nevertheless, that disaster lurks every morning as we turn on the machines. Careful calculations of the amounts of electrode paste and paper rolls suggest that we will make it, barely, through the survey.

The fog today is heavy and wet. The mud and filth, the screeching geese and grunting pigs and rattling wagons, the ruddy peasants and their rustic wives in patched trousers, all recall the coarse peasantry of Brueghel's paintings. On sunny days we have a particularly poor response and overall we have, so far, a low response rate here. This week, it appears that a nearby market fair has reduced us to a trickle of twenty-seven participants per day.

On the positive side, we are blessed with marvelous electrocardiographic technicians here, medical students I know only as Sabina and Velika, who are competent, hardworking, uncomplaining and, more important for me, non-singing! The pop song, 'Di pinto di bleu,' still rings in my ears from the incessantly singing technicians in Dalmatia. The Dalmatian cardiograms are now all mounted and I am plowing through their initial coding at the rate of forty-to-fifty per hour.



November 3

Despite the many problems, we have finished the survey in Slavonia with only one eligible participant missing. He is apparently at sea. Two myocardial infarct patients were identified by electrocardiogram. We had a wonderful time with Pentti Rautaharju, who works carefully and effectively and will soon come to Minneapolis, where we will finish work on our electrocardiographic coding system. Serbia, First round, 1962

The Serbian operation under Professor Djordjevic' began in 1962, at Velika Krsna (Black Cross), and profited immensely from the earlier Croatian survey experience, the participation of Srejko Nedeljkovic' in prior surveys, and the effective coordination and sharing of skilled staff. Thomas Strasser supervised and carried out much of the laboratory data collection, and, in 1965, came to Minnesota to develop the Serbian

data for analysis and publication. Bozidar Simic', pioneering nutritionist, carried out the diet surveys and food analyses. I directed the electrocardiographic station and was amazed to have to instruct the men, ages forty to sixty, how to ride the bicycle ergometer. They were as likely to pedal backward as forward. It was only after being reminded of the status of the roads connecting Velika Krsna with its neighbors that I realized these men had never used bicycles in their lives.

The Serbian surveys went so expeditiously that my journals lapsed during this period. I recall, however, that our team enjoyed going back in history on a visit to Topola-Oplenac, the historical repository of the Karadjordjevic' monarchy and the tomb of the last Yugoslavian king, Alexander, killed in Marseilles in 1934.

Croatia, Second Round, 1963

September 25

Today Pentti and I departed Munich in great spirits, navigating by Volkswagen van the Gross Glocknerstrasse and traveling down through Slovenia to the Adriatic coast.

The famous coastal road, described earlier as renovated by Napoleon 150 years before, is now sealed off for construction of a grand sweeping highway to Dubrovnik.

We are repeatedly forced onto detours through Bosnia-Herzegovina (the scene in 1995 of villages decimated by civil war). It is a barren moonscape with miserable terraced fields, scraggly orchards and vineyards, and dark, furtive children, dogs, and goats everywhere.

Poised on the cliff of the plateau above the Adriatic, we looked down at coastal towns far below, and at the shimmering sun on a magnificent sea, with the lovely blue arc of an archipelago on the horizon. At dusk we reached the coast at Sibenik, arriving during a grand naval gala. The entire Yugoslavian fleet was in port with its uniformed crews perambulating gaily on shore leave. We felt part of a Gilbert and Sullivan operetta. Makarska

The second round Seven Countries survey in Dalmatia in 1963 was accompanied by much social palaver, high-tech add-ons, and a great deal of staff enthusiasm and collegiality. The Research Committee of the International Society of Cardiology was at the acme of its influence, with Keys and White in charge. The leaders had arranged a meeting of dignitaries from around the world at our survey center in Makarska to produce a broad-ranging report with recommendations for needed cardiovascular disease research.

This added greatly to a sense of significance and to the festive and collegial spirit of the repeat survey in Dalmatia. The Makarska Conference of the international group culminated in a successful report, with only one hitch (described later in The Healing Power of Jazz).

This second survey round, I was determined to avoid illness and went through elaborate preparations, importing corn flakes, condensed milk and canned goods to last the duration, carried in our packed Volkswagen mini van rented in Munich. There, Rautaharju and I met his graduate bio engineering student, Hans Friedrich, engaged to prepare the high-tech electrocardiographic and other recordings being added systematically to Seven Countries field surveys.

The team works efficiently on this second-round survey. The young medical students are stimulated by

proximity to grand cardiologists. The staff are of many ethnic origins, and our evenings are spent in medical discussions, pleasant dinners, endless toasts, and late-night dancing.

Despite the problems of power outages and difficult transport along the coast – the usual hazards of working in Yugoslavia – things are going well. I managed to disguise my gastro-intestinal susceptibilities, until finally forced to eat anchovy and hard-boiled egg sandwiches, washed down with slivovica, with the mayors of each new village as we moved down the coast. This reduced my enthusiasm for the work that had to go on!

Slavonia, Second Round, 1963

October 15

Even the packing in Dalmatia and the transport to Slavonia seemed happier and sunnier in 1963 than in 1958. But now, on the Hungarian border, the mists roll in again. Ox-drawn carts lumber across rich, green fields against darkly wooded backdrops reminiscent of scenes from Doctor Zhivago. Again, we live and move in swirls of mud. Our participants, their harvest complete, become progressively dissolute, foul-smelling and lice ridden, eventually affecting our own spirits and health.

But there are a few bright spots here in Slavonia. We see nests of great, dignified storks in abandoned church steeples. Our country inn offers lunch of 'Fishpaprika' from a huge caldron, in which grease and paprika float on the surface while clumps of catfish bones and meat and tuberous vegetables protrude. We relish this spicy fish stew, served over grayish hunks of the local peasant bread.

At the confluence of the Donau and Drava, two great rivers of central Europe, we watched fishermen dock today during mid-day break. Smiling toothlessly, they held up their catch proudly for us to admire: wriggling, hammer-headed river catfish, magnificent, fifty-pound beasts of the deep.

Despite every precaution, I have again become ill. In my hotel room in Osijek, I am worse each night, with fever, chills, and dysentery, subsisting on the local mineral water – foul-tasting, bitter stuff. Desperate this morning, I happened to read the tiny print on the bottle label and realized I have been treating myself daily with several liters of a mild solution of Epsom Salts! Each liter contains nearly a gram of magnesium sulfate; hardly the best strategy for dysentery.

Again, I leave the field from Slavonia in a special rail car to Belgrade, then by a first-class Wagons Lits compartment to Munich, where I will find the cleanliness, calm, and care of the West.

Conclusions

The baptism by fire of the survey teams in the field was a dramatic and useful contribution of the Dalmatian component of the Seven Countries Study in Yugoslavia. This 1958 experience was crucial to all subsequent activities of the study: the methods, procedures, training, and attitudes and strategies were tested for carrying out difficult field operations. Moreover, Buzina's nutrition fieldwork in Yugoslavia was central to determining the contrasting populations examined in Dalmatia, Slavonia, and Serbia, greatly enriching the outcome of the study overall.

Buzina's international role in nutrition has strengthened the Seven Countries Study from the outset. Clearly,

his initial hypothesis about animal versus vegetable fat was a pioneering concept, which has been confirmed widely as having a central role in atherogenesis. In Yugoslavia, the diet measurement strategy provided the basis for precise ecologic correlations of diet and disease in the Seven Countries Study and other studies internationally.

Buzina's skillful organization was also responsible in part for meetings that have profoundly affected the course of cardiovascular disease epidemiology and prevention. The first was the 1963 Dalmatian meeting of the Research Committee of the International Society of Cardiology. At this meeting the subsequent research of that organization was born, as was its organization along lines of Scientific Councils. The 1968 Makarska Conference involved the International Society of Cardiology, the World Health Organization, and the National Institutes of Health of the United States. Its recommendations profoundly influenced subsequent generations of preventive trials and community-based studies. In addition, the first International Ten-day Training Seminar in Cardiovascular Disease Epidemiology was held during that 1968 Dalmatia survey, and this seminar has become one of the more effective training programs in the field.

Buzina has continued in his official capacity with WHO to provide broad overviews of Mediterranean dietary patterns and health issues.

The work in Serbia with principal colleagues Djordjevic' and Nedeljkovic' has provided the modern demonstration of the effects of rapid changes in population risk characteristics on subsequent disease experience. Serbia has had a phenomenally increasing coronary heart disease rate, at least up until the recent civil war.

Collaborators

The Seven Countries Study had, and still has two teams in Yugoslavia. Ratko Buzina is the Principal Investigator for the one based at the Public Health Institute in Zagreb. The other team, in the University of Belgrade Medical Center, was first headed by Professor Bozidar Djordjevic and now is led by Professor Srejko Nedeljkovic.

Ratko Buzina

Professor Buzina's nutrition unit is in the Zagreb University Institute of Public Health. He is a nutrition scientist of great repute, a thoughtful intellectual with a direct gaze and a charming, open demeanor, soft spoken, physically compact, and efficient.

Skilled and productive as a researcher, he has effectively collaborated over the years, yet retained a certain independence from the 'Keys' School.' He led an excellent nutrition and biochemical staff in his institute in those days, and through his contacts with Professors Arpad Hahn and Ivan Mohacek in the Medical Clinic, he was able to mount a skilled team for the inauguration of the Seven Countries Study surveys in Dalmatia and Slavonia in fall, 1958. He supervised one of the more complex field operations, in the face of great difficulties.

Buzina, now with the World Health Organization at Geneva, joined enthusiastically in the reunion of Seven Countries investigators held in Fukuoka, Japan, in 1993.

Ivan Mohacek

Mohacek is a powerful, impressive man physically, with a calm demeanor and intelligent face rendered

more thoughtful by wire-rimmed glasses. He brought to the field examinations a measured pace that accommodated amenities for each participant with thoroughness of observation. His efficient but orderly manner stabilized the team when it worked under pressure with many participants in poor facilities. His quiet critique of new survey forms and procedures led to stronger standard approaches for the study.

Over the years, Mohacek joined in other Seven Countries field surveys where his facility in English and effectiveness also lent strength. His companionship, especially while riding the rails with the American team in the railroad laboratory car, was a delight. Since those days, Mohacek has become a leading cardiologist, much admired in academic circles in Zagreb.

Bozidar Djordjevic'

There was also an international orientation among the Serbian team, personified in the graciousness of Professor Djordjevic'. Closely linked to the Tito administration through his high position in Belgrade University, he was able to facilitate the field operations and provide an effective staff for the surveys in Serbia. Rotund, soft-spoken, with an 'Old School' education and charm, plus fluency in French, Djordjevic' ran the operations from headquarters, as would a benevolent general. Two cardiologists, Srejko Nedeljkovic' and Vladan Josipovic', served as his effective officers in the field.

Srejko Nedeljkovic'

Nedeljkovic' has been a devoted and tireless colleague from the outset of the Seven Countries Study. A large, friendly, modest man, champion at tournament chess (his wife achieved even higher standing in chess circles), he was quietly and constructively critical in our surveys, insistent on completeness in recruitment and data collection. A stalwart of the international team, he visited many other Seven Countries survey centers, giving generously of his time and experience.

The longstanding support of Nedeljkovic', particularly his aid to implementation of new dietary surveys and the development of high-tech electromagnetic recordings in the field, has made a major contribution to cardiovascular disease epidemiology and prevention.

Nedeljkovic' continues his essential contributions to the study, including carrying out the unending mortality surveillance. We were fortunate to have his presence, too, at the Fukuoka 35th anniversary, and we stay in close communication, despite the sanctions on Serbia, through his American brother.

The Seven Countries Study: Italy

Why Italy?

Italy presented Ancel Keys and the Seven Countries Study collaborators with the prototypical Mediterranean lifestyle and its apparently healthy diet of grains, pasta, legumes, vegetables, fruits, olive oil, bread, and wine. Italy, in contrast to other Seven Countries areas, also has one of the great traditional cuisines of the world. Moreover, for the Italian investigator concerned with both regional and individual differences, Italy is not just one country or culture. The contrasts of Nicotera in Calabria, Porto San Giorgio on the Adriatic coast, Montegiorgio in the Marche hills above the coast, and Crevalcore in the rich delta of the Po River, provide abundant contrasts of northern and southern Italian eating patterns, heavier on meats

in the north and on legumes, pasta, and olive oil in the south.

Crevalcore, First Round, 1961

Field adventures in Italian villages began with Crevalcore (which I have loosely translated, Broken Heart), in Reggio Emilia, a region north of Bologna that has unusual Catho-Communist politics and classic Northern Italian cuisine. For medical historians, Crevalcore is the birthplace of anatomist Marcello Malpighi, 17th century “father” of histology and discoverer of glomerular corpuscles, the complex filtration system of the mammalian kidney. His life-sized likeness in bronze decorates the town’s main piazza, as well as the cover of the companion volume to this one: “The Seven Countries Study, an Adventure in Cardiovascular Disease Epidemiology.” An hour’s drive north of Bologna, in the fertile plain of the Po Valley, Crevalcore was inhabited by prosperous, proud, and – incongruously – Communist farmers. The region was chosen by our nutritionist colleague, Fidanza, as representative of the rich northern Italian eating pattern.

March 6 : “Uno Disastro, Enrico” (A Disaster, Henry)

The survey went as swimmingly as the accompanying wet March weather. On its first day, the team examined sixty men. We find in field studies that we must strike a delicate balance between over- and under-scheduling participants, to prevent chaos among the staff and ill-will among the hardworking farmers. Delays occur mainly at the primary interview and diet recall, or at the electrocardiographic and high-tech recording station. At any rate, we did a good job the first day, though it was a long and arduous one for all.

Night fell as we shuttered the Crevalcore survey center at the close of work. With it came a steady cold rain and blustery winds. Dead tired, two Italian medical colleagues and I set off in a tiny Fiat 500 toward the promise of comfort and dinner in the warm restaurant of the Hotel Bologna. In the back seat, I was decidedly uncomfortable as we careened along the slick, wet-black roadways, narrowly avoiding ambulant peasants dressed in somber grey capes and dark hats. We dodged between them and farm carts and bolted down the straightaways. I fantasized about the meal to come in the restaurant under the ancient arches of Bologna: twisted loaves of flaky peasant bread, a tangy radicchio salad, and an immense bolito, the traditional platter of boiled chicken, beef, pork, and lamb, washed down with a solid Lambrusco. Eventually, I dozed off in the back seat.

Some fantasies later, I was awakened suddenly by an awful thud, a shock, and a blast of cold wet spray in my face. Our tiny Fiat was swerving wildly, decelerating, finally coming to a stop in blackest night on the outskirts of a small town. In the front seat, my colleagues were profiled against a weak street lamp through a huge, jagged hole in the windshield. They began to shout hysterically: “Misericordia, Enrico! Accidente! Uno disastro! La bambina. Muerta!” This was followed by an incomprehensible stream of keenings and apparent cursings.

My dulled consciousness slowly awoke to the tragedy around us as my colleagues gestured frantically back up the roadway toward a tiny still figure in a puddle at the side of the road. I forced myself to be calm, if only to contrast with their panic, while they, paralyzed, hung onto each other and onto the steering wheel. I suggested that two of us go back to the form in the road and the third run to summon help. No one moved.

Finally, I pushed by them from the back seat, opened the Fiat’s door and stumbled up the street in the dim light in the rain, noting out of the corner of one eye a bright brass plaque reading “Dottore” something or other, on the gatepost of a villa along the way. I then came upon the crumpled bundle, a girl of about ten

years. An old peasant lady picked herself up from the side of the road and hobbled toward me, mumbling unintelligibly. Meanwhile, my colleagues remained in the car, transfixed and moaning. Nothing else was happening. No ambulance, no police, nothing!

Against my better judgement, fearing long delays in help, I gathered the unconscious girl in my arms and struggled back toward the bronze plaque which I now could make out: "Dottore Sergio Messina, Medico Practico." I rang the bell insistently until a distinguished, though rumpled, middle-aged man in a bathrobe appeared, also mumbling, at the gate. He took one look at the face of the child in my arms, then he, too, became hysterical, shrieking in Italian, "Horror of horrors, she is the daughter of my housekeeper. Is she dead?" We then moved together toward the villa, where he opened the portal and we entered, he wringing his hands, weeping, casting furtive glances at the still form in my arms.

I placed the little one on the doctor's examining table, repeating over and over, "Prego, ambulance, prego!" He would rush to the phone, then rush away, scurrying ineffectually about his cabinette, wailing "Sono solo, sono solo!" I, too, felt all alone, but proceeded to examine the girl. One pupil was large, but both responded to light. She may have had a head injury, but she wasn't dead! All her extremities were flaccid and the right leg drooped at an exaggerated angle, indicating a major hip or thigh fracture. Unexpectedly, she began to whimper, and then wretch. Not only was she alive, but was regaining consciousness!

My colleagues then appeared in the doctor's villa, still speaking in torrents. Finally one of them took the doctor's telephone and called the police and an ambulance. We all milled about, miserable, until the child was splinted and taken away to a hospital in Bologna. Then, summoned by the police back to the roadside, we underwent an official, if cursory recounting of the "accidente" and detailed measurements on the pavement to indicate the trajectory of the girl and of our car.

These good colleagues, as I have found is customary with all my Italian friends, drive their small Fiat projectiles on the open road with the accelerator floored. If the little cars were able to go 120 kilometers an hour, they were driven at 120. The terrible driving conditions of a dark, windy, wet night, and entering the outskirts of a village, were no deterrent.

The girl had started running across the street from the left, seeking we know not what. She was struck first by the Fiat's left front bumper, hurled upward to hit the windshield, shattering it. Then she was thrown to the top of the car, hurtled off to the opposite side, knocked down the old peasant woman passerby, and finally landed in the roadside puddle. No doubt these progressive decelerations explained her survival.

In the days following this awful event, my otherwise bright and charming colleagues continued to refer to the event as, "uno disastro, Enrico," implying an uncontrollable event, an act of God. The only culpability, it seemed, was the girl's, darting across the street on a rainy night. That we were driving too fast on a dark, wet night through a village, simply never seemed to enter their minds. Nowhere, moreover, were these facts noted by the village policeman who became obsequious when the Professori Dottori introduced themselves. Later, the rationalizations led to an apparent absence of concern. To my knowledge, nothing further was done about the injured girl and her family, other than sad shaking of heads. I hope, however, that my knowledge is incomplete.

At any rate, I often wonder whether that little girl is now a happy Italian matron and mother of beautiful children, or possibly is a professional, perhaps even an especially compassionate orthopedic surgeon. Or, might she be a crippled recluse in a barren institution somewhere?

I will never know.

March 8

Back in Crevalcore, not a word was spoken about this horrible stain on our mission. There was no discernible effect on the community's attitude or level of participation, as far as we could tell. The survey settled into an efficient routine for a full three weeks. The Italian team, certainly less stoical than the U.S., Yugoslav, Dutch, Finnish, or Japanese teams, nevertheless worked together effectively. Team members were quick to identify bottlenecks, and resolve them, and respond to the usual daily confusions. And our evenings at the Hotel Bologna were a delight.

In Crevalcore itself, the long mid-day break became the most pleasant part of the long work day. We would visit Trattoria Julia, little more than a "hole in the wall" with tables for a dozen people and a tiny, narrow kitchen with open gas burners. Julia prepared exquisite dishes, especially a spinach lasagna. Unfortunately, I had three strikes against me as far as Julia was concerned. I was American and non-communist; I spoke little Italian; I was not possessed of the gigantesque appetite of my Italian colleagues. Eventually, however, Julia accepted me, probably because I was such a faithful, if modest, customer. The whole team delighted in the ambiance of her place, the banter, the aromas, and the elegant meals.

Evenings in the team's Bologna hotel were usually productive as we reviewed the day's survey activities and made suggestions for improvements. Northern Italian cuisine, served until late in the brightly lit dining room, included huge plates of fresh pasta lightly scented with butter, olive oil and herbs. This was washed down with a light, red wine, and complemented in texture by the flaky twists of local bread. Lightly broiled fish, skillfully de-boned by our cheerful waiter, was followed by a huge traditional platter of boiled meats.

On evenings when I felt less sociable, I holed up in my room, playing saxophone along with Sydney Bechet records on a boisterous Italian portable record player. It was there that I learned "The Egyptian Fantasy," "Passport to Paradise," "Waiting for the Day," and other expansive Bechet ballads. It was the first year of my romance with an old Conn soprano, still my favorite horn thirty years later. These evenings, accented by a Dewars with San Pelligrino, without ice, provided a marvelous release from the grueling monotony of days in the field. I became known in the Bologna neighborhood as "Il Maestro Musico," receiving a kind, if bemused, tolerance.

March 10

It appears that alternating current interference is with us permanently, with no alternative locations available for the electrocardiographic station. Nevertheless, the station is highly efficient; average time for an electrocardiogram from start of a case to start of the next is only ten minutes. The average time from the moment of stopping exercise to starting the precordial lead record is thirty seconds, and to completion, another fifty seconds.

We have seen two typical old anterior myocardial infarctions in the first hundred participants at Crevalcore, a case of malignant hypertension with fundal papilledema, macular star, and hemorrhages, and one diabetic with capillary aneurysms.

My job of training and early supervision here is nearly done. I will leave behind extensive guidelines for colleagues Mohacek and Tedesco on electrocardiographic recording and trouble-shooting, and on criteria for standard clinical coding.

March 22

We hit case number 600 today in Crevalcore.

Montegiorgio, Second Round, 1966

Anche Uno Disastro! (Another disaster!)

In the spring of 1966, the Seven Countries Study was in the midst of the second round survey in the villages of Montegiorgio and Porto San Giorgio on the central Adriatic coast of Italy. There, we met Pentti Rautaharju and his engineer colleague, Herman Wolf, as well as members of the Yugoslavian and Italian Seven Countries field teams. It was a big year for our recording of electrocardiograms by new methods, on magnetic tape, at rest and in exercise.

I was met at Rome's Fumicino Airport by an Italian colleague in a Fiat 500 like that involved in the earlier adventure near Crevalcore. We took off toward the Apennines, our car loaded with survey equipment. A rosy Alpenglow gleamed off the snow-covered peaks as we climbed eastward over the spine of Italy. Just as night fell, starless and moonless, we arrived at the divide, the Adriatic far below. My colleague paused a moment at the pass.

Then down the mountain we went, freewheeling, in top gear. On the straightaways, at top speed, the clutch went in "per conserve di benzina," and as we wildly approached the turns, the brakes were slammed hard. We teetered and screeched around each curve, turn after hairpin turn, and then again hurtled down the straightaways. There was no idea of driving in gear, no idea about shifting down for powered turns.



Black became the night. Suddenly, on an inside curve, the little Fiat's overheated brakes locked. We skidded wildly and hurtled off the highway into the blackness!

At the turn just above, there was a 1,000-foot drop into a ravine. At the turn just below, a 500-foot plunge into a dark stream. But at our turn, we left the road, sailed over a greensward, tumbled over and over, and came to rest gently against a soft hillock.

Silence.

Then came the now-familiar cry, "Uno disastro, Enrico! Accidente! Misericordia!"

My door was jammed, but I was able to extract myself through the cleanly broken window. Then, as an obstetrician might do with forceps over the



head of a plump baby, I inserted first left hand, then right, helping deliver inch by inch the ample flesh of my colleague through the tiny Fiat window. Delivered, he knelt in the green field, shivering.

Abruptly, out of the silence and darkness, loomed a band of peasants in silhouette. After commiserations with the good “professore dottore,” and assurances that we were intact, they together picked up the little Fiat and carried it the hundred meters back to the road. There, setting it down like a clothes basket, they stood by patiently as we surveyed the damage. Unbelievably, only a dozen test tubes were broken among some \$30,000 worth of equipment. And we were fine.

Our helpers then pulled out fenders gouging the tires, and we proceeded down the mountain, limping, scraping, veering crab-like at a few miles an hour until we reached the next village. Companions hailed, our equipment transferred, the remainder of the trip to our hotel in Porto San Giorgio was uneventful.

Grateful to be alive, I silently swore that I would never, ever again ride as passenger in a private automobile in Italy.

Conclusion

The Italian Seven Countries Study experience confirmed the salubrious nature of the Mediterranean lifestyle and eating pattern. It highlighted the effects of different lifestyles within the varied geography of Italy. The Italian collaboration, particularly that of Fidanza and Puddu, was centrally involved in the initial concepts, hypotheses, and methods of the Seven Countries Study, as well as in the selection of Italian and Mediterranean survey areas. A major field pre-test of the Seven Countries Study protocol, instruments, and methods was carried out by Fidanza and an international team with Keys and White in the fall of 1957, in Nicotera, Calabria. Most of the later Seven Countries principal investigators met there.

The added Italian surveys and two-year follow-up, plus the Italian Rail Study, contributed significantly to the precision of data and the development of methods for the long run.

Menotti has been centrally responsible for the coordination and analytical team that so effectively held the study together following the end of the National Institutes of Health support in the late 1960s. His analyses and collaboration with Keys and the other Seven Countries investigators have revealed the remarkable findings of multivariate prediction of coronary heart disease risk, regional differences in prediction of absolute risk, and comparable findings in the magnitude of risk (coefficients) for long-term compared to short-term coronary heart disease experience. In recent years, the Italian center's contribution has been in understanding the effects of changes in distribution of risk characteristics during the first ten years of Seven Countries surveys in regard to subsequent cardiovascular disease experience. This has established unequivocally and for the first time – using standardized, comparable methods – that the shift in risk characteristics in either direction, favorable or unfavorable, is associated with parallel shifts in population rates of disease, after a certain lag time.

In addition to these major contributions, the Italian studies were clearly the first epidemiological enterprise of any sort on population-based samples in that country, and the first to show the independent significant predictive power of conventional risk factors within the Italian culture in regard to death from coronary disease, cerebral vascular disease, other causes of death than cardiovascular, and all causes of death.

As much as any other study, the coordination of the dietary and medical surveys in the Italian component of the Seven Countries Study resulted in a universal understanding of the healthy nature of the so-called "Mediterranean Diet." It also revealed the importance of dietary patterns, over and above single foods or nutrients, in determining the population-wide causes of disease and death.

Collaborators

Flaminio Fidanza

Fidanza was the first major Italian collaborator of Ancel Keys. They met during Keys' 1951-52 Oxford Sabbatical, spent partly in Naples where Fidanza was a young academic nutritionist. Through Fidanza's local contacts, they were able to recruit clerical workers and executives of Italian banks and industries to carry out the first informal population comparisons relating diet to blood lipid levels.

Fidanza was and is a devoted, passionate Italian academician, harboring strong professional opinions based on a long career of research and field experience in nutrition and in methods of measurement. Bombastic, great-hearted, and warm with his friends, he can be sharply critical of those who fail to meet his high standards. Portly but quick-moving, he is always at the center of attention. But Fidanza is a careful listener and a "quick study," always responding enthusiastically, with only a tinge of Old European intellectual skepticism and a trace of Italian fatalism. Tales abound to illuminate the emotional side of his nature. But professionally, he is immensely informed, with great bench savvy and practical experience in the field. There is no nonsense when Fidanza directs, or is even involved in a survey; he is a fierce cloud one moment, a warm ray of light the next.

Fidanza's curiosity led him to explore, incorporate, and elaborate on many of Ancel Keys' ideas. His skepticism led him to question them as well. I suspect that his persistent dogging of Keys with the idea that U.S.-Italian differences in blood cholesterol levels were not entirely explainable by fat composition of the diet contributed to the series of careful metabolic ward explorations of Keys and company. These were carried out in the University of Minnesota Laboratory of Physiological Hygiene through the 1960s, using fruits, nuts, complex carbohydrates, vegetables, and fibers, while holding fat and calories constant. It may also have been Fidanza's persistence about individual differences in blood lipid responses that encouraged Keys' pioneer explorations of the intrinsic level of blood cholesterol and the variability of individual responses to a given dietary change. And it was surely Fidanza's gregariousness and acquaintance with foods, people, and places in Italy that principally determined the choice of Italian villages in which to test the dietary hypotheses.

It was a delight to have Fidanza in the Laboratory of Physiological Hygiene for the better part of a year in the late 1950s, when he was a bachelor and life of the party among younger faculty and graduate student gatherings. We were all pleased, of course, when he found his quietly competent Italian bride, Adelberta, who shared his knowledge of the laboratory, complemented his skills, and softened his restless impatience and acerbity.

I think of Fidanza mainly as leader, critic, and stimulus. He is always on target with a well-timed welcoming or celebratory toast, a salutatory introduction, a learned dissertation, or a sentimental eulogy. But I also remember him for the beauty of his language. In Fidanza's speech, every vowel is rounded and musical, every word intelligible, every phrase original, every sentence elegantly but simply constructed, and every message sparkling clear.

Fidanza was, from the outset, one of the “seminarists” living in the community called Minnelea on the coast south of Salerno. He was one of the originals responsible, along with Vittorio Puddu, for finding the property that they all bought advantageously in the middle 1960s and share so graciously today with colleagues Ancel Keys, Jeremiah Stamler, and Martti Karvonen of Finland.

In recent years, Fidanza has become preoccupied with the duties of his chair at Perugia. Unfortunately, we see him rarely at international cardiological gatherings. He has reverted to nutritionist type. He remains, however, a leading Italian light, an international figure in his field, and deserving of great credit for the success – conceptually and practically – of the Seven Countries Study and its operations in Italy.

The thirty five-year reunion and conference of the Seven Countries Study, arranged by Toshima and Koga in Fukuoka in October, 1993, was graced by Flaminio’s and Adelberta’s presence. There, he forcefully insisted that the monograph recently prepared by the investigators and edited by Kromhout, Menotti, and me, should not see light without his rigorous edit. When, aside, I remarked to Adelberta: “Flaminio really hasn’t changed, has he?,” she replied with a resigned but affectionate smile, “Unfortunately, not at all!”

Vittorio Puddu

Professor Puddu, now departed after a long illness, was ever gracious, calm, and dignified, fully as Italian as Fidanza, but in the manner of “il grande padrone.” It was he who gave our team access to the hospitals and to the recruitment of young colleagues, Mario Mancini, Alessandro Menotti, Bruno Imbimbo, and Salvatore Panico. And it was he who chaired the Seven Countries Study working conferences in Rome. It was also he who provided quiet and effective leadership to the International Society of Cardiology, without putting himself forward for acclaim or for the presidency. It was he who introduced us Minnesotans to the grandest and to the simplest of Roman restaurants. I recall particularly the deep-fried baby octopus and artichoke, specialties of a tiny restaurant in the Jewish Quarter where he was so admired. And I recall the most elegant Roman restaurants where he presided with grace, regaling us with stories of La Bella Roma, pre-World War II, when, as he said, that magnificent city was just a big town. He helped us to imagine Rome with all its ancient history and beauty, yet with the calm of the 1920’s and early 1930’s Ñ and a population of only 250,000! That would be as delightful a prospect as, say, living in San Francisco during the same Belle Epoch.

Vittorio Puddu, victorious, kind, dignified, and physically grand with his beige suits and bronzed bald head. He was elegant down to his toes, and to his traditional Christmas gift, a special Italian coffee cake.

Mario Mancini

Mario Mancini was the earliest collaborator of the second generation of Seven Countries Study investigators. He is now distinguished Chief, Medical Clinic II, in Naples, editor of a new journal, Chair, International Society and Federation of Cardiology Scientific Councils, and dignitary in cardiovascular and metabolic circles in Europe.

In the 1950s, as a young protégé of Puddu and clearly destined for leadership, Mancini was one of the early post-doctoral fellows to arrive at the University of Minnesota Stadium Gate 27, working on projects in hemostasis and lipids. There he was frequently amazed with middle America, the quiet calm of our lives, our confidence in our professional futures, and to him the unexpected richness of our family life. Overwhelmed also with mid-western orderliness and manners, particularly on the streets and roadways, he marveled at how people drove with such courtesy to others; without anger, pride, or showing off.

Mancini, no longer active in Seven Countries data or its field work, remains a superb host for gala celebrations in Anacapri for Ancel and Margaret Keys and the Seven Countries collaborators. He remains a steadfast friend of the study, and an international leader in the field.

Alessandro Menotti

Menotti, too, was a fellow in cardiology under Puddu in Rome, and became progressively involved in the Seven Countries Study through an assignment to the Italian Railroad Study, a collaboration between Henry Taylor and Puddu. Solid, calm, hardworking, meticulous, and intellectually curious, Menotti was the ideal person to be responsible for quality control and coordination of the Italian Railroad Study, and later, of the Seven Countries Study. Happily, he was given the field organization, data collecting, and data editing responsibilities after the first series of five-year Seven Countries surveys. At that time, taken up with crucial concerns for new activities at the Minnesota base, I agreed, “carte blanche,” that Menotti take over coordination of the data gathering and develop collaboration in analyses with Keys and the Seven Countries investigators, a collaboration that has proved smooth and productive.

Menotti, recently retired from his high post in Rome, has currently the position of Visiting Professor at the University of Minnesota, which promises continued productivity and collegiality for the Seven Countries Study.

The Seven Countries Study: Greece

Why Greece and the Islands?

The special knowledge of Greek team leaders, Christ Aravanis and Andy Dontas, and their colleagues, students, families, and friends living on the islands of Corfu and Crete, provided the background for the scientific questions addressed there.

The chief question was the long-term effect of a diet high in fats, mainly monounsaturates, but low in saturated fatty acids. The theory that saturated fatty acids are the principal cause of mass elevation of blood cholesterol and thus, of coronary heart disease, was therefore addressed in the Greek Islands under the special condition of a high-fat, low-saturated-fat intake.

Questions about the alleged life-giving, mystical properties of olive oil also could be tested stringently. The Greek Islands share the salubrious Mediterranean environment and characteristic eating pattern: occasional meat and chicken, more frequent fish and seafood, and staples of grains and starches, legumes, vegetables, and fruits.



Aravanis, Dontas, and collaborators brought to the study their special interest in the metabolism and respiratory physiology of aging populations. All this, along with gaining Ancel Keys' and Paul White's attention, and Aravanis' influence and independent funding, made the Greek collaboration crucial and the Greek Islands a desirable Seven Countries region for study.

The beauty of the Islands has captured Western imagination since the Iliad and the Odyssey. But, in reality, the poor and scattered villages of the Greek Islands created major logistical problems for the study. Only with the help of the masterful, Zorba-like team leader, George Arniotakis of Crete, were these obstacles overcome.

Crete, Second Round, 1965

A pilot study in Crete in 1957 confirmed the feasibility of a study there, but due to delayed funding, the formal surveys began only in 1960, and then without Minnesota participation. First-round Greek survey data were locally collected in a standard manner, however, edited in the field, and forwarded to Minnesota for collation.

In Crete, in the fall of 1965, an international team met in Iraklion to schedule the second round survey, mainly operating out of Hotel Xenia. The survey team was compatible and very "Greek," loving and extolling their land. Together, we enjoyed meeting the dark "pappas," the old men of the villages, exploring their healthy diet and dignified lifestyle. We shared with them a lemonade or an ouzo in a local tavern, and listened, with appropriate skepticism, to the political rantings from Athens Radio broadcast in the square.

In those days, the men of Crete walked or rode bicycles to their fields or vineyards. It was only with the ten-year follow-up examinations that they acquired three- and four-wheeled motorized carts. Television was not yet a major influence, and even electricity arrived only with the ten-year survey.

We of the survey team were captured by the beauty of the arid, rock-strewn plateaus of Crete during the grain harvest, when the grain was winnowed in stone circles by the feet of men, or by women in black dresses and shawls, pulled around field circles by donkeys. With our own "Zorba," Arniotakis, "George," we traveled to high pastures in which men enjoyed each other's stories and on Saturday danced at midnight under the bright moon. We understood then the fictional Zorba's madness over the mystery of Crete. Our hearts, as his, welled with a love of life and of fellow man, as we worked in this stark, timeless land.



On workdays in the villages, we were amused by the hordes of scrawny Cretan cats on rooftops, or scurrying along every whitewashed wall. We were fascinated by peasant women nonchalantly knitting while riding their donkeys side-saddle, returning from the distant hills with large bundles of faggots.

We marveled at the potter's family on the lower side of Thropsanon, who maintained a centuries-old tradition of producing huge clay urns for water, wine, and oil. These were formed with an incomprehensible precision, without any visible measurement.

We watched the evolution of an entire ceramics process: molding by hand on the potter's wheel, cutting the soft clay with a string, adding the simple signature pattern of the family around the circumference,

sun-drying two halves of the urns, firing in the kiln, and finally, the emergence of great Minoan-style vessels.

We were amazed by the apparent cleanliness of the island villages, where, in fact, everything used was biodegradable.

In a land bathed in sea breezes, baking under the sun, and host to numerous scavengers, such cleanliness is natural. We watched the wine-pressing carried out in a traditional manner with bare feet in great tubs. On the plateau of Termidion, we saw thousands of cream-colored windmill sails turning softly in the evening light.

In Crete, we were mesmerized by the cicadas, sawing away at progressive frequencies as the day heated up, slacking off in the cool of dusk.

We enjoyed the donkeys' bray and the calls of the whippoorwill and nightingale at dawn.

We were enchanted by a purple sky melding into a dark sea, a softly lapping surf, and sunlight dappled through grape arbors as we gathered to rest and chat during the long siesta.

We were fascinated by the preoccupation to obtain water in a dry land, and by the lushness of oases where water is artfully conserved, using ancient techniques. We found shade under panoplies of olives, grapes, or, on the southern coast, bananas.

The pastoral life of the island has changed little for several thousand years, and continues comfortably side by side with the ancient ruins of Knossus, Matala, and Phaestos, sites of the Minoan civilization. In ancient times, the high priests and upper classes lived in handsome palaces, in symbiosis with the peasantry, each class accepting its role.

Modern elements have affected mainly the region around Xanes and its British naval base captured by German parachutists in World War II. It became a post-war American naval base with an Armed Forces Radio and TV network. This influence in the 1960s was largely limited to the trade area west of Iraklion, and we felt little of its impact on "our villages" in central and eastern Crete.

The major products of Crete – grapes, fruits, and vegetables, and olives and olive oil – remained the major products during the baseline, five- and ten-year Seven Countries surveys. During these years, the Seven Countries Study was able to tap the essence of traditional Greek Island culture. Since that time, Crete has been invaded by mass tourism, and many lifestyle changes have resulted.

September 2 : Crete

Mohacek and I took off by car at 3:30 p.m., driving north to the sea through Avdou, a valley lush with vines, olives, and gardens, and spring-filled streams. We then climbed to the plateau of Thermidion. The plateau is now accessible by a good road, but we took the old road up the western flank where the final pass is dominated by ruins of huge windmills once used for milling grain. At the crest, however, the entire plateau opened before us, and, like an immense field of daisies in bloom, 20,000 windmills irrigating orange groves turned lazily in the slanting yellow light of late afternoon!

Villages around the periphery of the plateau are connected by crisscrossing trails. Seemingly prosperous, happy peasants dwell in this world apart. It is too bad we are not studying heart disease in this stable

community, with its rich heritage, good crops, and long isolation. There should be enough hillside villages around the world to compare fitness in places where people must daily climb hundreds of stairs, compared to plains dwellers. On foot, we scrambled up a hill and explored deep into the “Grotto of Zeus” by candlelight, a cold, damp, unremarkable cave except for the pleasant view of light reflecting on wet green moss.

Crete is a grand island, from the yellow dust of the southern coast, to the palm forest of the east, through the shaded oases in the northern valleys and the miles of mountain carriageways. Potentially, it is as prosperous as California, favored by sea, sun, and just enough water and soil. It cradled the elegant Minoan culture of old, the civilization that disappeared overnight, presumably due to the eruption of the volcanic Thera.

In this season, as the parching of summer stretches into fall and the grapes are harvested, the land has turned from a green carpet to a beige caldron. On the Libyan Coast the dust swirls around our feet in eddies like turbulence in a mud-bottomed lake. There has been no rain for months. A three-year old child drives a blindfold mule in a circular path, raising well water for irrigating vineyards. An adolescent girl rides a donkey sidesaddle in a circle, knitting unconcernedly, lifting water from another well for vegetable gardens. There is a great peace, still, in this ancient land.

Despite my lack of knowledge of the language or culture, I feel a deep affection for Crete. Some day, I hope that my children will gambol about these hills. It is satisfying to have a firm friend on the island, in the noble figure of George Arniotakis Aracondis.

Samaria: Eighth Wonder of the World

September 7

My major responsibilities to the Crete third round survey completed, I invited Noboru Kimura to join me for adventures on the western end of Crete. I wanted to climb Mount Ihda, the mystical mountain that figures in Greek mythology. Was it another home of Zeus? Was it the launching point for Icarus on his fateful flight? I don't recall. I was determined, nevertheless, to climb that mountain. For some years, I had also wanted to see what the Cretans call the eighth wonder of the world – the fabulous Gorge of Samaria. Noboru was ready to commit the several days needed for this expedition. We took off toward the sunset in a rented VW Beetle.

I am forty-five and Noboru close to sixty. We are both in reasonably good shape, but not what you would call “in training” for our hurried weekend expedition to the highest and lowest points of the island of Crete!

Despite multiple maps, we never found a trail up Mt. Ihda; we simply barged directly up its flanks. Even though we had high-top hiking boots, it would be hard to imagine a less pleasant hiking experience, stepping from one sharp crystalline limestone boulder to the next, brushing vicious brambles each step, mercilessly beaten by the Aegean sun. We had cleverly chosen high noon to start our scramble amongst the Cretan Alps!

Even the summit of Mt. Ihda was elusive. It was difficult to tell whether one ridge dominated another and whether we had actually reached the top. With walking sticks stuck into the rocks and decorated with our caps, we took multiple documentary pictures, as if we had reached an important summit.

The light clouds, afternoon shadows, and long swigs from our canteens gave us energy for the trip down. In

the Beetle, we took a long, winding route into the mountains of western Crete as the shadows lengthened. The chalet at Omalos, near the head of the gorge, was a welcome sight. So were the beer and simple fare we downed before retiring.

September 8

Over breakfast this morning we were regaled with the lore of the Samaria Gorge by the chalet keeper who read to us epic Greek poems about the people of the gorge, the Sfakions. They dwelt in villages along the Libyan coast, and for centuries, their principal access to the northern coast was directly up the gorge. Historically, they were apparently a ferocious race of Cretans, keeping largely to their own affairs, fishing and farming along the coast, hunting in the gorge, living in isolation from the rest of the island's commerce and culture. Their epic poems had to do with hostile tribes to the north – how they would plan their attacks, estimating the weather and then slipping up the gorge by moonless night. It's an eighteen-kilometer hike from the Libyan shores to the head of the gorge. The Sfakions always struck unexpectedly, avenging the putative wrongs done them, then stealing back through the gorge. Their forays were timed to occur before a major storm, so that, when followed by vengeful warriors, their pursuers would be caught in flash floods at the point where the gorge narrows to two and three meters, the Iron Gates.

These spine-chilling stories from an ancient past were reenacted during World War II, in a daring raid similarly planned and executed against an entire company of German parachute troops in their barracks near Omalos. The Germans were slaughtered to the man by the Sfakions, who then escaped down the gorge. The raiders were well hidden and dispersed before other German troops could take the long detour around to the southern coast and search for them with boats and patrols.

Nobu and I got an early start today down the gorge, first in Alpine country along pleasant trails and wooden steps (Xyloskalon). Down we hiked, each step against the hard limestone trail resounding in our ankles, knees, and hip sockets. We used muscles that are almost never conditioned – the going-down muscles of mountaineering.

The gorge narrowed progressively and the craggy cliffs obstructed more and more light as we descended the canyon. At the halfway point, the gorge abruptly widens to a pleasant meadow at the abandoned village of Samaria and its Venetian church of Santa Maria dating from 1379. There, we encountered the only two living beings of the entire trek. We had been warned not to fraternize with any locals we met, but a gregarious Japanese and American could not avoid waving at the beekeepers.

They gave not the slightest response to our gesture. Clearly, we were unwelcome invaders.

For the rest of the course, we were in and out of the stream, in and out of delicious pools of clear, cool water, drinking and bathing and soothing tremulous muscles and burning feet.

Then again, down and down, crossing the stream on boulders to find paths always on the opposite side. The boulders became ever larger and smoother from centuries of rushing torrents. The canyon became ever narrower, its walls menacing on each side.

Down the way we could see it narrow to the eye of a needle at the "Iron Gate" (Sideroportes). Passing through the gate, the canyon walls again opened up and we scrambled over tumultuous boulder fields the last few kilometers to Ayla Roumeli, a deserted village on the site of an ancient Temple of Apollo.

We fairly skipped with joy at the end of this long, hot, and pounding march. There on the beach was the

little white hut we had heard about, with its lovely vine-covered lattice. We found relief in tall mugs of beer, hot soup, bread, and olive and feta salad. We were the only hikers of the day and the innkeeper had no idea if or when a boat would come along the coast to take us to Khora Sfakion where we might expect to find a bus back to Xania and civilization. Somehow, we didn't worry, and lay on the shore in the late afternoon sun. Our bellies stuffed, the fatigue seeping from our limbs, we dozed, like proud lions after the kill.

Just at sunset, we heard the distant putt-putt of a fishing boat rounding the point. Its captain responded to our vigorous hailings from the beach. The drachma note we waved as he pulled ashore seemed to bear the appropriate denomination and, with no other formality, we waved adieu to the innkeeper up the beach and were off around the coast to Khora Sfakion.

September 9

Today we traveled by bus through Xania, back to the chalet at Omalos and our VW Beetle. By this time, Kimura and I were firm friends, having had adventures, and suffered, and celebrated together.
Corfu, Third Round, September, 1971

During this fall's survey, our team enjoyed observing the Corfu olive harvest. Nets were spread around the bases of the trees and a young lad climbed to their tops to shake down the fruit. The crop was loaded into wagons and taken directly to the oil dealer. There, the olives were washed with well water, cold-pressed and filtered through cotton batting to remove twigs and foreign bodies. With no chemical treatment, the oil was then funneled directly into cans; the golden olive oil of Crete. I sprained my back taking a large container of it from an olive press all the way home to Minnesota.

Later, we stuffed ourselves on freshly harvested almonds, almost to the point of cyanide poisoning.

In this survey I encountered the local pride of a Corfu taxi driver who claimed that Spiro Agnew was a Corfuote (the driver's name, too, was Spiro). He avowed that America must be the most wonderful land in the world to have a Corfuote as its Vice President! This occurred some time before the ignominious fall of Mr. Agnew, and then, of his President, Nixon.

Glyfada in those days was a largely "undiscovered" beach on the west central coast of Corfu, reached by a steep rocky road. During breaks in the survey, I kept my journal there, played saxophone, and grew a new beard while staying at a primitive beachside inn.

The Corfu survey operation went so smoothly that my journal became largely travelogue.

Corfu, Second Round, 1966

Corfu surveys in the 1960s were confined to villages at the northern tip of the island, where olives were the predominant crop and olive oil export and tourism the principal commerce. After Venetian times, cultural dominance alternated between Italy and Great Britain. There was inter-marriage of the royal Greek families with both colonial cultures. The major nineteenth-century British colonial presence in Corfu left a residue of ugly Victorian architecture.

In the second-round Seven Countries survey in Corfu in 1966, the island was relatively unspoiled. The colonial powers were gone, King Constantine had his summer palace there and a few other aristocratic

families were left. Most of the island remained inhabited by farmers living their time-honored lifestyle, but Corfu surveys were more difficult to organize because the people were more touched by foreign culture, tourism, even by labor unions. Nevertheless, Corfu remained a lovely, peaceful Ionian isle, extending from the magnificent bay and peninsula of Corfu City and lowly mudflats in the south, to the imposing clay falaize and natural arches, caves, and beaches of Sidari at the northern tip of the island.

Kastelli, a village north of the city, was our principal operational base. We resided in the comfortable Villa Castello and dined under the twinkling light of its chandeliers. We operated the survey northward and westward to Paleokastritsa on the coast, the most romantic harbor of the island. On Corfu, there was a chronic problem in recruiting participants and meeting schedules, due apparently to an inherent resentment of officialdom by the farmers. Intensive diplomacy was needed in which the local Orthodox priest helped break resistance to the study. Once a few men had come in for examination, and reported back how they were amused by it and well treated, the rest flocked in. Field director Arniotakis was central to the successful recruitment. In the photograph below he is engaged in earnest debate with the elderly, toothless mother of one of our invited participants. When Arniotakis convinced her of the value of the study, the errant son appeared soon after.

The Corfu diet in the '60s was the highest in fat of the Mediterranean countries in the study, twenty-two percent of daily calories came from monounsaturated acids, most of them from olive oil. The farms were larger and more automated and the men slightly heavier, and we had the impression of a lifestyle less traditional than that on Crete. But from a survey perspective, Corfu was more compact, transportation was easier, the meals were less primitive, the accommodations were more comfortable, and the Corfu team was more mellow and experienced. Corfu relatives of Dontas, and of my wife, Nelly TrocmŽ, lent a special local charm and hospitality to the 1966 survey.

During the customary extended mid-day pause, the northern beaches and bays of Corfu were exquisitely suited for private bathing. Coves could be reached by rented fishing boat, and there we bathed in the sea and enjoyed a pleasant lunch of Greek delicacies. After a restful nap we returned to the vigorous evening examination schedule. Our long survey days usually ended with a late night banquet at Villa Castello.

September 1 : Korakiama

The atmosphere of Corfu seems especially suited to “civilized” endeavors and repose. One is stimulated, not enervated. A light sea breeze mingles salty sea with sweet jasmine. Gentle shade provides relief from the ever-present sunlight. The appetite is finely whetted. Crusty, coarse peasant bread is broken and dipped into the delicate golden Corfu olive oil, spiced with succulent black olives.

The double days of Greece seem to double one's effectiveness. For example, good day's work is accomplished between 7 a.m. and 1:30 p.m. Then, because of the human size of the communities, people can return to their homes at noon. There can be a dip in the sea, chats and snacks in sandals and robes, a shower, a light lunch, and a nap in a cool, shuttered room on coarse linen sheets. Then there's a bath, a new shave, and a new workday that starts around 4:30 p.m. and lasts through the height of commerce, until 7:30 or 8 p.m.

Vacationers read, write, explore the narrow streets of the town,

shop in the bazaars, and watch the parade of life in the streets. Whether working or on vacation, cocktails and dinner with family and friends begin at 9 p.m.

Dinner may be followed by pleasant conversation, a stroll under fragrant pines and a bright moon, and reading. In the night, we hear a distant donkey bray, then a near-by owl punctures the calm with a startling hoot. Through these two different, complete, fruitful units of the day, the life span seems, indeed, to be doubled.

This romantic view of life in the islands contrasts strongly to the experience of our colleagues in Athens, which is more characteristic of modern urban life in the West.

There, academic chiefs build powerful, exclusive fiefdoms, modified only by revolutions, juntas, and other social upheavals. I have heard of one medical chief so proud he will not present a hospital clinico-pathologic conference without foreknowledge of the pathological findings! Aristotle would surely turn in his grave.

For the younger physician in Athens, medical life is a series of frustrating days in and outside the hospital. These begin with early meetings to plan the day with the staff, a visit to the administrator's office to beg for funds for minor repairs, and repeated ward rounds, followed by a frantic drive at noon across a congested, polluted city for a harried family lunch. Then come several hours of private practice out of the home, which allows for survival on an academic salary. Later in the day, young doctors return to the hospital for emergency rounds and, if able, to conduct their research.

September 6

Today we queried routinely one of our subjects on this lovely island. The bright-eyed, wizened gentlemen replied proudly to our question about his occupation: "The hardest work on earth," he said, "and the most beautiful. I am fisherman!" Poet, peasant, and nobleman combined.

September 8 : Kastelli

I am always shocked to hear the desperate, convulsive plaint of the donkey's bray, trailing away as it does in pitiable sobs. The sound is probably as natural and meaningless as a yawn, but to me it seems a shriek, expressing dumb incomprehension and the burden of being a jackass! Is it simply a response to some discomfort, such as hunger? Is it a basic language among isolated animals? Or is it a primal cry of some lost soul reincarnate?

Crete, Third Round, 1970

August 15 : Archanes

In this old village, we had twenty-four subjects the first morning and everyone was in a panic. There seems to be no use repeating over and over, "Please, only a half schedule the first day." Each area team has to learn its own hard lesson, it seems, in each new village.

The sun and the katydids recall the reverberations in Van Gogh's Provencal paintings. I frequently check my face, not believing that sunglasses are really in place. I remember no such overwhelming brightness since Florida childhood. The cicadas started buzzing promptly at 7:10 a.m. today. I will time their concert again tomorrow. Watching closely I see no motion in their legs, which I had thought produced the vibrations. When their sawings hush in the evening, the strange sounds that replace them soon become familiar: the bray of a donkey; and a musical bird whose song is as regular as a metronome – every three seconds.

Archanes is situated on a promontory above a lush valley. There's a minor peak to the west and a major mountain range in the distant east. Our lodging, Hotel Dias, is a kilometer above the village. The region is known for superb table grapes and for women of rare beauty. We are here during a minor feast celebrating the Virgin Mary and the grape harvest. The people are in a festive mood.

August 17 : Thropsanon

We set up clinic on Sunday afternoon in Thropsanon Major, a sizable village. Its mayor, in straw hat, baggy britches and boots, invited us for coffee at the local tavern. We visitors, curious about the community, directed many questions to the mayor. Instead of translating them for us, our good colleague Aravanis would try to answer them from his own, sometimes incomplete knowledge.

The customers in the tavern were cordial, Sunday-clean, and were having little or nothing to drink. In fact, we see no public drunkenness in any village. The children often gathered about the team, delighted with my "magic" – the disappearing coin and disappearing lower teeth tricks (a prosthesis).

Our survey headquarters is clean and adequate and all should go well here. The local beer is awful, the Minos white wine heavy and sharp, but I am looking forward to trying the red. The bottled water is bland, the cuisine peasant-poor and greasy but edible. Evaporated milk on my self-imported Grape Nuts for breakfast keeps me going until noon.

The roads to Thropsanon are macadam most of the way. Motoring about this part of Crete is great fun but hazardous because of the locals' propensity to drive on the left side of the road. Arniotakis jokes: "It's only the Communists that drive on the left side."

Mosquitoes, usually rare, are out in force tonight. I can't quite determine whether the lady mosquito's rump is parallel or obliquely elevated on biting, the sign of Anopheles. Both filariasis and echinococcus disease occur here, plus typhus, malaria, and even sand fly-borne kala azar. We'll do well to take care against insects, and against uncooked food.

The streets are clean, but all privies are exposed, with only a tiled floor and hole. This makes the moderate fly infestation disconcerting. How sad it is that we don't export metal screens instead of Coca Cola. What a major public health contribution the United States would make to introduce screening of privies about the world.

Crete is greener, more prosperous, and seemingly happier than I had anticipated from earlier experience. But tourism will surely become more important here and new roads are already strongly influencing lifestyle. All-purpose, motor-powered carts are evident and, of course, television is on its way.

Our colleague, Adrian Corcondilas, is warm, intelligent, intense, and passionately Greek. His vocabulary and ability in both French and English are imposing, as are his knowledge of Greek history and interest in

the sea. I look forward to good visits with him. He and Lekos run the cardiac cath. lab in the Department of Cardiology at Hippokrateion Hospital in Athens.

This evening, we went with Amiotakis to search for a missing subject, a villager who had moved to Iraklion. We found him in a side street, working in his pottery shop. There we were able to watch this master craftsman, taught by his father and grandfather before him, perform a craft that will surely die with this generation. Pottery is being replaced by plastic and aluminum.

For the moment, there is still a market for the traditional urns, because many maintain that oil never spoils in natural clay vessels. Construction of these vessels is called “angioplasty,” the same word we use medically today for the repair of blood vessels.

In vigorous, coordinated motions, the potter kneads the reddish clay, wetting it on the base, turning the stone with a sure rhythm. He can produce small vases, ashtrays, urns for oil, and incense containers at a rate of one a minute. He models for us both open and closed containers, destroys them, and makes still others for our amusement. He presented me a Minoan-style ashtray with apologies that the painting and glazing were not as tasteful as they should be.

During lunchtime today we watched the local potter in Thropsanon make huge vessels for olive oil and water out of coarser clay and with a much lighter-weight flywheel. He is another master craftsman, in a tradition unchanged for thousands of years. He uses prickly sage to fire his kiln, and the scene around the kiln is a delightful chaos of ancient-style vessels in various stages of completion.

On my noon wanderings about the village many locals ask to be photographed – a common request in “primitive” cultures everywhere. One lad wanted to be taken shooting a slingshot; another held up a dead mouse tied by the tail to annoy the girls. A little girl wanted her picture taken with a live cicada buzzing away between her fingers. An old veiled woman in black, occupied in the shade of her house, wanted to be pictured cutting up strips of rags for quilting.

In these villages, as in Dalmatia, a number of older men have returned here to their homeland after years of employment in the United States, mostly it seems, in Pennsylvania. One complained bitterly that Carnegie Steel at Homestead still owed him two weeks pay! When I promised to present his grievance to them on my return, he seemed little interested. Perhaps this would ruin the good story he has plied for thirty-five years.

George Zoumboulakis, a charming villager, invited us onto the veranda of his tavern this morning where there is a glorious view over the church and fields to the eastern mountains. He said in good English that he had returned to Thropsanon because, “Everybody loves the place where he was born.” How beautiful it must be to see, at age seventy, where one played at age ten, and to be a part of the continuing life in one’s natal community. Our host recounted the legend which all citizens of Thropsanon firmly believe – if someone should fall into the church well, the water will rise and throw them back safely. More believable is the claim that water from that well, used in baking, causes the bread to rise without yeast.

August 21 : Kastelli

We have reached the town of Kastelli after a beautiful drive through the rocks on a eucalyptus-lined roadway at the western edge of the mountain range. Though not as breathtaking a site as Thropsanon, this city, on a paved road, is more important and the dispensary more adequate. The survey work goes well.

We have here in Kastelli a new problem for the survey. Fathers often register children as several years older when they are born – an average of one or two years. It has something to do with military service eligibility, but certainly confuses record keeping.

Mohacek and Menotti are experts at electrocardiography and it goes well here. Because of the participant “parachutists” in the younger and older age range, we will have a good sample for age-trend studies. In the “department of field improvisations,” we are cutting the urine dipsticks longitudinally to double their number because we are running short. We have found that a systematically high hematocrit reading was due to cleaning with saline instead of acetone between cases. This has been corrected.

August 27

Back in the survey center today, through translation by our spirometry technician, a local peasant described to us a Cretan arranged marriage. Though there is no formal written agreement, the pact is never broken. Any party breaking it, said the man, would be beaten to death by the other villagers (shades of the stoning in “Zorba”). He attempted to impress on us the necessity for the trial period of marriage, which concludes when pregnancy occurs. This makes good sense evolutionarily, but is strictly in the tradition of male supremacy, of “blame the woman,” and rejection for infertility!

We had a pleasant lunchtime today in the square of Kastelli with Ancel and Margaret Keys joining the survey team under lush berry trees. The Keys feel much as I, a bit out of place without direct responsibility in the survey work. There is less satisfaction in standby supervising than in participation. Aravanis’ team and our Minnesota group could use a little more imagination in exploiting our visit, if only for professional “stimulation.” But in “Latin” fashion, our Greek colleagues have gone to great effort to ensure that we are “comfortable and amused,” rather than involved and useful.

Conclusions

The Seven Countries Study findings in the Greek islands have had a profound influence on research and thinking in cardiovascular disease epidemiology and on eating pattern and lifestyle approaches to prevention and health promotion. They not only confirmed the salubrious nature of the “Mediterranean Diet,” but they provided a major lesson – not yet “a shot heard round the world” – that an habitual eating pattern relatively high in fats is compatible with good health, low cardiovascular and cancer risk, and substantial longevity, under the particular conditions of the Greek diet. That is: high in fruits, vegetables, grains, legumes, complex carbohydrates and fibers, low in saturated fatty acid intake, and high in olive oil.

Moreover, the study’s findings in Greece have profoundly influenced our understanding of the physiologic and health effects of monounsaturated fatty acids and olive oil. They have significantly altered the course of nutrition research in the United States and internationally. Many details remain to be worked out, including the overall risk of high total fat and high-energy intake versus output in relation to cancer risk.

The Greek studies have also made special contributions to understanding the effects of mass change in population risk characteristics and their predictive importance. The data on trends may contribute to explanations of the rapid acceleration in cardiovascular disease deaths reported recently in WHO statistics for Greece.

Collaborators

Christ Aravanis

The cardiological units, hospitals, and medical factions in Athens are beyond my ken, but Aravanis represents the grand, traditional Old School. I suspect that he is politically conservative, while medically liberal.

Aravanis has a long face with sad eyes and the dignified demeanor of a senior consultant. He has shown clear vision and authority over the years, implementing effectively the Seven Countries Study undertakings in the Aegean and Ionian isles. Aravanis also had access to the Orthodox priests of the islands.

One of the more colorful photographs of the Seven Countries expeditions (above) shows Ancel Keys bowing low, in an exaggerated Japanese style, before a dark, handsome, unbowed priest on Crete.

Priests hold remarkable power in their communities and they provided great credibility to our efforts. Aravanis put together a staff of younger colleagues he had trained in cardiology, including Demetrios Lekos and Adrian Corcondilas, plus nursing faculty and local practitioners. He was able to augment the meager Seven Countries allocations with local staffing, housing, and transportation.

Aravanis met Ancel Keys in the early 1950s at a meeting of the American Heart Association in Chicago, where Aravanis trained and found his bride, Tula. He was invited to join Keys and White on their first trial run, in Nicotera in southern Italy, in the fall of 1957. Directly thereafter, he escorted the pilot survey team by DC 3 from Athens to Iraklion.

A classic photograph (below) shows the team of pioneer investigators lined up on the dirt airfield along the sea in northern Crete. It included White, Noboru Kimura, Martti Karvonen, Aravanis, Dontas, Keys, Flaminio Fidanza, and their spouses.

Aravanis has remained a steady colleague in the Seven Countries Study. Even though his politics were not always in line with the Greek military junta or the subsequent political swings in Greece over the last twenty- five years, he has managed to keep the Seven Countries Study operation going on a shoestring – sufficient to follow the five- and ten-year formal surveys with continuous mortality surveillance up to thirty years. He has presided over independent and collaborative developments of the Seven Countries Study data.

Strong in the clinic and an international leader in cardiology, Aravanis has participated vigorously in the new science of cardiovascular disease epidemiology. He is among its insightful pioneers.

Andy Dontas

“Andy” is the diminutive anglicization of “Anastasios.” Dontas was educated in Athens and at the University of Michigan. A bright, sensitive, and enthusiastic investigator of wide interests, and a worrying perfectionist, Dontas provides the ideal complement to the sober Aravanis as co-investigator for the Greek studies. His industry and his personal researches in gerontology are a driving force to independent publications from the Seven Countries Greek populations. A frequent visitor to the Stadium Gate 27 Laboratory and Division of Epidemiology at Minnesota, he remains an active participant in field studies in Greece and in the other Seven Countries areas.

A charming and effective colleague, Dontas deserves credit for the practical operations of the Greek team and for much of its intellectual stimulation. He has provided the glue between Greece and Minnesota, professionally and collegially.

The Seven Countries Study: Finland

Northern Europe: Why Finland?

Forty years ago Martti Karvonen and Ancel Keys were convinced that Finland held a key to understanding mass atherosclerosis. They were quite right.

Here was a peaceful, rural land of hard working farmers and loggers, having traditions of close family ties and rugged independence, and with singular freedom from the stresses of Western industrial society. Yet, fatty artery disease was rampant.

Heart attacks, strokes, and claudication were well-known phenomena prior to World War II, but not epidemic until the long privations of wartime Finland were relieved.

In the countryside, it was essential that men eat calorie-dense foods. One could hardly cut trees, strip bark, pile logs, or till stony fields and bogs during a short growing season, all under inclement conditions, by “chewing one’s cud” or eating sprout sandwiches.

Loggers’ lunches, even today, are things of wonder, unsurpassed in caloric density: Large hunks of meat are suspended in congealed fat, enveloped in a dark bread loaf fully permeated by fat. The whole – at 250 grams of fat and well over 2,000 calories – is packaged in aluminum foil and tied with a ribbon. This hefty fare is preceded by a breakfast of fish soup, containing fifty percent butter fat calories and several grams of salt. The evening meal provides the rest of the 6,000 calories the logger needs to work outdoors all day.

Finland provides the clues, the tests, and the strongest arguments that the major socio-cultural influence on heart attacks and mass atherosclerosis is a diet of highly-saturated fatty acids from milk and meat fats.

Finland provides the primal ecologic evidence for the dietary cause and prevention of mass fatty artery diseases. East Finland departs from the regression line on the high side, that is, it has an even higher rate of coronary heart disease than expected from the overall Seven Countries population correlation between diet, blood cholesterol level and coronary heart disease.

In contrast, the West Finns have less coronary heart disease than expected from their average cholesterol level. There may be differences, as claimed by Finnish pathologists, in the internal caliber of the middle muscular layer of coronary vessels in the East Finns. Whether this, if true, is due to exposure to atherogenic lipids or represents the difference between the Ugrian origins of East Finns versus the Scandinavian origins of West Finns, remains at issue.

On the other hand, if oxidized low density lipoprotein is a major factor in its pathogenicity, then the East Finns’ coronary heart disease level is compatible also with the paucity of anti-oxidants and trace minerals in their foods and diet. Vitamins A, C, and E are consumed in relatively small quantities. Moreover, the soil of East Finland lacks selenium, so that even the few fruits and vegetables the Finns grow and eat are

deficient in anti-oxidants.

Moreover, the Finns have high levels of iron, an oxidizing agent, in both their diet and blood serum.

Therefore, the individual correlations within Finland, and the regional differences for ecologic analysis, still provide a rich opportunity for testing major hypotheses about atherogenesis and thrombogenesis.

The relative and absolute intakes of omega-3 and omega-6 fatty acids also fit hypotheses about the roles of hypercoagulability and platelet function in atherosclerosis and hypertension. Moreover, physical activity shows a U-shaped distribution, with higher rates of cardiovascular disease in those Finns who are little active as well as at the other end among those engaged in heavily active occupations.

Finland provides the classic example of the importance of the mass determinants of population rates, over and above the individual's risk of disease. For example, the high general level of occupational and leisure time physical activity, and high levels of measured physical fitness in Finland, fail to prevent the ravages of high population levels of blood cholesterol. The latter becomes the necessary cause of mass atherosclerosis.

Though the picture in Finland confirms the major causal hypothesis about the role of dietary saturated fatty acids, a basic issue remains, as exposed in a practical dietary experiment completed some years ago. Can the picture be changed? East Finns were placed on an Italian diet and Italian farmers on a Finnish diet. As in the black and white prisoners that Keys and John Brock of Capetown studied in Southern Africa forty years before; the groups rapidly approached the blood lipid characteristics of those in the adopted eating pattern.

These findings recall the admonition of Jeremy Swan, distinguished clinical scientist from Los Angeles, who once said to me: "It's ridiculous, Henry, to think that a process as complex as atherosclerosis can be attributed to or changed by such a simplistic matter as habitual diet!"

I have great respect for such people who explore "the baroque beauty of biology" in its infinite perplexities. But I must admit to greater admiration for the distinguished clinician or scientist who sees the whole picture, not just its complex parts, and who realizes the importance of simple ideas and even of "simple research" on those ideas. For example, the terrible biologic complexity of metaplasia and carcinoma in the bronchi would, of course, largely disappear with one simple (?) public health measure – cessation of cigarette smoking.

The evidence is also strong that fatty artery diseases disappear, or fail to appear, in populations having habitual diets that produce population cholesterol averages less than 190 mg/dl.

At any rate, the "natural experiment" of Finland was, and is, a fertile field for research by Keys and company in the Seven Countries Study.

East Finland, Second Round, September, 1964

The five-year follow-up in Finland in 1964, started with the East Finnish cohort in Ilomantsi, a country village serving a large farming and logging area along the Russian frontier.

The Finnish survey team worked effectively amidst the calm beauty of that land. The participants were hard-working and seemingly happy people, close to the earth, laboring in the forest and fields, and on the endless glacial lakes. They came to our border guard survey station from many kilometers around.

For this survey, the local investigators, led by Karvonen, planned an international conference on methods for assessing physical activity and fitness in populations.

Henry Taylor from our laboratory played a major role in organizing the Minnesota contributions, and in the course of the conference paid his first visit to the Seven Countries Study international surveys.

Once the conference and social activities surrounding it were over, the field team turned to its survey task with enthusiasm. The border patrol station, which housed the guards and their activities at the Russian frontier, was released to the examination team for the several weeks required to complete the survey of some 800 East Finnish men.

There was an especially elaborate protocol for the examinations in 1964, with add-ons of psychosocial questionnaires and psychomotor testing by Alan Barry and his group from Lankenau Hospital, and of bicycle ergometry with computerized exercise and standard rest electrocardiography. Rautaharju, Hermann Wolf, and the Dalhousie team also made recordings of heart sounds, chest wall excursions, and pulse wave velocity, the beginnings of what we anticipated would be routine high-tech evaluations for epidemiological field studies.

For some years at that time, I headed a U.S. Public Health Service Heart Disease Control Program Sub-committee on exercise electrocardiography and physiologic methods. We were full of grand ideas about how to get objective, continuous measurements in whole populations having different risk of cardiovascular disease. From experience in the U.S. Railway Study and similar undertakings, we should have been less sanguine that the high-tech approach would soon produce data in a usable format. Thirty years later, however, the methods sewn then are finally bearing fruit in the activities of Rautaharju's Epicore group.

The Finnish international survey team took to its task with vigor. The local field workers had prepared well for the survey. Led by Karvonen and Orma, they were resourceful in dealing with the unending series of unexpected happenings: power failures, equipment failures, and people failures. The Finns, a serious lot generally, have a streak of sardonic humor, which makes collaboration in field activities most pleasant. Moreover, they always have an eye toward the "R and R" time that must come in every field operation. Five or six twelve-hour days of a steady load of fifty to seventy examinees a day was about the limit before a break. Three weeks of this grind, and a significant hiatus is needed so that staff can return, at least briefly, to their homes and offices.

A Country Sauna

Pirkko (now Siltonen), our chief survey technician in 1964, was the Finnish "den mother," vigorous, competent, cheerful, and gregarious. Though dead serious about the survey work, she always had mischief in her eye. It was Pirkko who saw to it that the initial interviewers established rapport with the wonderful Karelian men, some of whom had ridden bicycles many kilometers to the station for their examination.

These interviewers were able to seek out, diplomatically, the information that Pirkko wanted for the "social good" of our team. She sought farmers and loggers living in the countryside who, in our brief contact with them, had shown a good feeling toward the study and the team, and who would reveal what kind of country

sauna existed on their property.

Eventually, we decided that this question was also appropriate to the formal part of the activity questionnaire, because the sauna is such an essential part of Finnish lifestyle. At any rate, in time, Pirkko had the desired information in hand.

The first weeks' examinations having gone on for seven days running, one of the interviewers came into our electrocardiographic station one morning dangling before our weary eyes an old-fashioned key – the key to an isolated wood sauna far off in the autumn landscape of Karelia. Plans were laid for a sauna party that very night.

When the medical part of the team arrived at the moonlit farm, led by Pirkko, we found a dramatic nighttime scene. Lanterns hung on boughs about the sauna, a cheery fire blazing inside, with everywhere the lovely fragrance of wood smoke – birch and pine. Wrapped in moss in a pail was a packet of leafy birch branches of uniform length and maturity, picked, we were told, in mid-June and carefully stored. Pirkko grasped them in her happy arms and plunged them into a bucket of cold lake water.

Soon we heard squeals and giggles from inside the sauna. According to custom, the women had arrived earlier, prepared the fire and were taking their sauna before the extreme temperatures had been reached. As the men disrobed in the nearby woods, the women poured out of the hot house, ran down the dock and plunged into the lake, splashing about with shrieks and laughter. Quickly climbing from the water, girded in towels, they rushed into the dark to change into warm clothes and start preparing our picnic meal.

Now it was time for the men to take the “real” sauna. The Finns wet themselves down while the visitors stayed dry, and we entered to face a searing blast of hot air beyond any previous experience. Visitors were encouraged to take the lower benches, but we chose the higher ones so as not to appear weak. There, eyes shut, breathing shallowly, we adapted gradually to the beauty and fragrance of the searing envelope.

All were silent at first, emitting only occasional grunts and sighs. Opening our eyes to peek through the subdued light, cardiologists and physiologists were reduced to the same parboiled, common denominator. Karvonen, our sauna-master, ordered us out after only ten minutes exposure, to sit quietly on a bench outside where we watched the distant silhouettes of the women around the camp fire.

Then the men returned to the torture for a second round, the temperature having soared another notch in our absence. In preparation for the ultimate initiation, the novitiates were again strongly encouraged to sit on the lower benches, then instructed on what would happen and how to behave. It turned out that the instruction was wholly inadequate to deal with the actual experience.

When a bucketful of water hit the bed of blistering rocks, it vaporized explosively, rising to the top of the sauna where our colleagues on the benches above held their breaths, immobile. Suddenly, the steam layer reached our level with an incomprehensibly scalding heat. One dared not breathe, sparing the lungs. After a first gasp we held our breaths as long as possible and expired as slowly as possible, until, after a few seconds, the worst was over. Then we broke into a profuse sweat.

Our leader extracted the leafy birch twigs from the water bucket, laid them momentarily on the sizzling rocks, and then proceeded to flagellate himself, and us, on the neck, back, shoulders, arms, buttocks, thighs, legs, and feet, bidding us do the same. Under the fragrant, stinging shock, every sensory ending is illuminated, firing at its maximal amplitude, creating an exquisite pain.

Then someone opened a beer and sprayed its contents on the sauna rocks, the hot, yeasty steam enveloping us until we could no longer stand it. We all burst simultaneously from the heat, ran down the dock, and plunged into the lake. There, the whole mass of tingling nerve endings was reactivated by the shock of the frigid water. Neurosensory endings stimulated so maximally cannot distinguish cold from hot, but can only respond with a fury of sensation.

I left the water quickly, feeling nauseated and faint from what must have been massive arteriolar constriction in the skin, plus a bradycardic dive reflex and major redistribution of blood volume.

After a few minutes of quiet sitting, an elevating calm invaded. Vitality crept back into our bodies. We towed off gently, cooling down slowly. Beers were passed around, and, feeling ever more mellow, we dressed and gathered around the campfire for food and conversation.

We visitors were impressed, for life, with the trial by fire of this near-sacred Finnish ordeal!

The Fit Finns

The East Finn survey participants make long travels by boat, bus, truck, car, and often by bicycle to come to our examinations at the border station. One of the remarkable things about them is that they are quite fit, yet their arteries are heavily involved with atherosclerosis. Finally, the disease becomes manifest by angina or cardiac infarction.

These men have a lifetime high level of fitness as a result of their vigorous occupations. It seems incongruous, but is highly significant, that a population with one of the highest rates of vascular disease recorded should have, perhaps, the highest level of fitness and live in rural calm and order.

The Finnish men we examine have lined, open faces. Though not as gregarious as our Mediterranean subjects, they move through the survey stations with good humor, quick to smile and to respond to greetings. The Finnish language is distinctive, with a staccato sound, clear and bell-like, full of vowels. It is pleasing off the tongue of the young women technicians, clipped and semi-swallowed by our medical colleagues, and a deep, bearish growl from the mouths of our hardy participants. These voices together create a soothing harmony throughout the busy survey stations.

I suspect there are different degrees of culturally determined motivation and competitiveness under stress. The Finnish men, for example, appear genuinely challenged by our exercise tolerance test, giving it “their all.” Alan Barry’s scale of perceived exertion is graded consistently lower here than in other Seven Countries areas. On a scale of one to fifteen, the same level of activity might be perceived as an eight by the Finns and a thirteen by the Italians, though these comparisons have not yet been made systematically.

Similarly, with pulmonary function tests, the Finn technicians are vigorous and the participants highly responsive, making all-out expiratory efforts. It is also likely, as our London colleague, Geoffrey Rose, has found and we confirm with his chest pain questionnaire, that there are sizable cultural, as well as biologic differences in responses among men of our Seven Countries regions. Comparative population studies do not resolve all the fundamental issues about “nature versus nurture.”

The New High-Tech Cardiovascular Disease Survey

The second round examinations in Finland are the more technologically advanced of all surveys up to now, 1964. Rautaharju and Wolf have developed solid and reliable systems for the recording simultaneously of multiple-lead electrocardiograms, phonocardiograms, chest displacement curves, pulse wave velocities, and pulmonary function curves.

As an interested collaborator and long-term sponsor of such technical undertakings, I observe that the instrumentation seems to be forever obsolescent, new instruments taking precedence over the old, new ideas and questions consistently displacing the old questions or recording modes, before the last are thoroughly exploited.

The epidemiological need for consistency, comparability and stability of measurement, and the academic need for published results, are superseded by the new idea and the new recording system and all its technology, or so it seems to me.

When I undertook these collaborations I had expected that we would soon have inexpensive and efficient “black boxes” to tie on to people to record and integrate respiration with heart beats, electrocardiograms, and pulse waves, giving continuous read-outs and even predictions, all in reliable, rugged systems.



It would be fortunate if such systems existed so that we could finally move into the modern electronic era of physiologic data collection, processing, classification, and prediction in population studies. But clearly, this was sanguine.

A Renaissance Man in the Forest

The field team of the Seven Countries Study, in Karelia in the Fall of 1964, was pleased, after three long weeks of survey work, to learn of an invitation to dinner at the home of the local pharmacist, who I'll call Pentti Saarinen.

His pharmacy, which served a large area of Eastern Finland, was based in Ilomantsi, a small logging and farming village of 1,200 inhabitants. Former mayor and still leading citizen, it was not unusual that he would honor our crew. Our survey was surely the town's major social event of the year.

The Finnish survey team was particularly serious, hard working, and effective. In three weeks they saw some 800 men, ages 45 to 64, first examined in 1959. After many days of a grueling schedule, with little social life on evenings in our simple country inn, the team was ripe for “R and R,” and we were quite lively as we walked through woods to the home of our host.

We found ourselves welcome and comfortable in the Saarinen's bourgeois home, sipping sherry before the evening meal. At dinner, all twelve members of the survey team were accommodated around a large oval table in the formal dining room, cheerily served by Mrs. Saarinen with her best china and silver.

The conversation was animated as we worked through several courses, starting with hors d'oeuvres of smoked reindeer tongue. There was considerable speculation about the radioactive Cesium content in the

meat of reindeer, which graze on Lapland pastures contaminated by Russian nuclear test fall-out.

At the close of the meal, our host offered tea selections from five large tins. In a personal, practiced tea ceremony, Saarinen steeped the type of tea appropriate to our requests, or, if no preference was expressed, he decided for us. All the while he explained the gustatory and pharmacological properties of each brew. It was a thorough, learned, and pleasant formality.

After tea and mints, we were offered a profusion of homemade liqueurs, accompanied again by a colorful lecture on each. He first explained his legal access to neutral spirits in the pharmacy, combined with a hobby of collecting herbs and berries. This seemed to us a reasonable avocation for a pharmacist, particularly one living in an isolated village fifty miles from the nearest state-run liquor store.

Our host first held up each handsome container, with its colorful herb or berry displayed, and then described the preparation and unique qualities of each brandy. Then, charmingly, he served each of us our choice concoction, catering to our curiosity and taste, making this, too, a rich experience.

The men team members were invited to carry their snifters to an anteroom, while the women, in the custom of those days, cleared the table and chatted. The gentlemen were offered choice imported Havanas from a musty wood humidor. The conversation by now had largely lapsed into Finnish and I occupied myself by strolling around the library and inspecting myriad photographs mounted on the wall.

In each was our host's beaming countenance, usually holding an impressive string of Lapland salmon.

Stupefying, however, was the identity of his fishing companions in the photographs. In one was President Kekkonen of Finland, in another, Chairman Bulganin of the Soviet Union, in another, Prime Minister Churchill, and in another, could it be — President Roosevelt?

All bore delighted smiles, with cigarettes or cigars at jaunty angles in their faces, holding one end of a string of champion fishes, our host holding the other!

When I reopened the conversation in English, I suggested quietly that our host was either a master of all master spies in history, or the most sought-after fishing guide on earth. Saarinen modestly admitted to the latter, and instantly rose several more rungs up the ladder of his visitors' esteem!

Cigars and brandies finished, our host rose and invited us to another salon, where we were joined by the women-folk, distributing ourselves in clusters of stand-up conversation. Again, I undertook my lone inspection of displays around the walls. Framed, under glass, were dozens of mounted specimens of colorful trout and salmon flies, clearly assembled by an expert fly-tier – our host. It all seemed to fit. Long, winters' nights brewing exotic liqueurs and tying flies to send as gifts around the world to his prestigious summer fishing companions.

We were then all invited to a rich, mahogany-paneled library, to examine bookcases filled with stamp albums. We were no longer intimidated, just amazed and curious about the next marvel. Harking back to my adolescent experience in stamp collecting, and minor specialization in United States postage issues, I focused on his American album, turning the elegant pages in wonderment. Every issue was there, complete, in mint and canceled form, missing only the rarest Upside-down Airmail and misprinted Pony Express issues.

This collection, far in the Finnish woods, was one of the top collections of United States stamps in the

world, in impeccable condition and beautifully displayed. One could only assume that the rest of his international stamp collection was equally choice and cared for. This was another example of the perfectionist and scholarly qualities of our host, and of his broad curiosity, collector's skills, and passion.

The female members of our team were beginning to yawn and talk about how long a day it had been. A very long day, indeed, and a lovely evening. Mrs. Saarinen was quick to take the cue, and suggested that she accompany the women the short distance back to the inn.

As our colleagues and hostess filed out, Saarinen offered us men glasses of French cognac, inviting us with a twinkle in his eye to what he called the "piece de resistance." He led us down the hall to still another library. There, we found an exhibit far beyond the experience of any of our team. In fact, it was quite beyond our ken. We were presented with immense, handsome, leather-bound volumes with onion-skin paper protecting priceless lithographs of classical erotica, dating back centuries. As we turned the enchanting pages, we were also offered objects d'art: amber in voluptuous shapes, ivory tusks carved with gracefully entwined bodies of men and women engaged in erotic activities. Nothing was offensive to the eye or touch. The difference was sharply defined between pornography, which I have always found repulsive, and classic erotica, which portrays the art and the central meaning of lovemaking in human activity throughout history.

Finally, excusing ourselves with our charming host, we walked the short trail back to the inn, shaking our heads and clucking our tongues in wonderment over this quiet, rotund, balding, kind, small-town pharmacist. Bon vivant, gourmet, companion of world leaders, expert fisherman and fly-tier, philatelist non-pareil, and finally, connoisseur and collector of erotic art!

The Sequel

Many years later, at a pleasant social evening arranged at the Paavo Nurmi Symposium in Helsinki, our host, Martti Karvonen, skillfully arranged a visit of conferees with President Kekkonen in the main salon. The vigorous old man had recently lost his wife. The month before, he had presided over the Helsinki Conference on Human Rights.

Kekkonen was full of himself that evening, exhilarated over the successful signing of the Human Rights Accords, enthusiastic about the significant role a small country can play in human affairs by sticking to principles, addressing central human issues, and showing imagination and enterprise. The aging diplomat-soldier, near retirement, seemed happy to spend the evening with physicians and scientists from around the world. He was in fine story-telling fettle.

Karvonen had arranged that we guests would each move forward unostentatiously around the President's table at intervals of several minutes, so that small groups of two or three people would have nearly private conversations with the President. As my small group approached the grand figure, I had a moment of panic about what we would talk about. Then came the idea to bring up mutual experiences with Hubert Humphrey, recently dead, a friend of so many great leaders and long a friend of Finland and its people. But suddenly it dawned on me to recount the story of Saarinen, Renaissance Man in the Forest.

I introduced the tale by saying, "We may have a mutual friend in Ilomantsi. A gentleman whose name escapes me invited our research team to his home some years ago" – and then I went on to the story of that evening in Karelia. I had not yet gotten to the fishing photographs when the President laughed, slapped

his knee and said, “Oh, you are talking about my dear friend, Pentti Saarinen, of course.”

President Kekkonen went on to finish the story for the others; his friend’s mastery of cuisine, brewing of tea, confection of liqueurs, salmon fishing with the world’s great leaders, fly-tying, stamp collecting and, yes, his loving collection of classical erotica.

These presidential reflections, years after the original event, were a delightful sequel to one of my more remarkable adventures in the field!

Conclusions

Much of the excitement and anticipation of Karvonen and Keys about the contribution of the Finnish cohort was realized.

The findings in Finland have had a profound impact on cardiovascular disease epidemiology and prevention. They established the world’s highest coronary heart disease rates (for the 1960s) among the East Finnish men. They illustrated the overwhelming role of a high-saturated-fatty-acid diet in mass elevation of blood cholesterol levels, the principal population cause of atherosclerosis.

The findings strongly affected thinking about population versus individual causes of coronary heart disease and led to research on why rates in East Finnish men are greater than predicted from their blood lipid levels.

The Finnish “natural experiment” has also revealed important contributions of anti-oxidants and minerals and perhaps iron to cardiovascular disease risk. Equally influential has been the revelation that an active outdoor lifestyle and high levels of occupational activity, within a relatively calm, stress-free environment, are not protective against high population rates of cardiovascular disease in the presence of a grossly atherogenic diet.

Finally, the Seven Countries Study in Karelia had the unexpected side effect of motivating the population of that region to inquire into the lifestyle and modifiable origins of their severe disease burden and to mobilize community prevention efforts. The resulting North Karelia Project starting in 1972, was the first major community-based program of cardiovascular disease prevention and health promotion. The Finnish story is not yet finished!

Collaborators

Martti Karvonen

Karvonen is a physiologist of the classical school of applied physiology – an expert in work, exercise, and sports physiology – and an internationally renowned physician. As Surgeon General of the army he was physician and advisor to President Kekkonen for many years.

A “quick study,” Karvonen sees relationships immediately. He’s also quick to see the potential of an idea or of a young investigator. For decades, he has produced a constant flow of research ideas and served as a stimulus to and supporter of innumerable research careers over the years.

Gregarious, vivacious, with sparkling round eyes in the classical open face of the Eastern Finn, Karvonen is wiry, dynamic, and could run all day and dance all night.

A devoted Seven Countries Study collaborator, he was an independent investigator who organized Finnish population studies as early as 1956. He later recruited the Seven Countries cohorts in Eastern and Western Finland to compare the separate cultures within that country.

Long active in the Research Committee of the International Society of Cardiology with Keys and White, he has also been a consultant to the World Health Organization from its outset. He was the behind-the-scenes organizer of the North Karelia Project, the first major community project to try to reduce risk of heart attack. In typical Karvonen fashion, he sparked the idea, mobilized the power structure, found good young people, and gave them responsibility and support. In that project, he advanced the careers of Pekka Puska, Jukka Salonen, and Kalevi Pyorala, as earlier he had done with Pentti Rautaharju, Sven Punsar, Jaako Kjihlberg, and countless others.

In the course of a long and active career, he initiated innumerable physiological studies and well-crafted epidemiological studies, clinical trials, and community research projects. He was, in fact, the “father” of many careers and of many new fields of scientific endeavor.

Karvonen and his wife, Anika, were original members of the famous Minnelea “Seminary” of nutritional and cardiovascular disease epidemiologists located on the southwest coast of Italy. Karvonen, at seventy-five, remains a scintillating and wise colleague, a sound investigator, and a powerful engine driving cardiovascular disease epidemiology and its sister, exercise science.

Sven Punsar

Punsar is a more typically taciturn Finn, though he is easily provoked to laughter. He is a dedicated clinician and cardiovascular scientist. Punsar made the pilgrimage to the University of Minnesota Stadium Gate 27 early, in the summer of 1958.

He, Rautaharju, and I worked under the stimulus of Keys and with the support of Ernst Simonson, to concoct, compile, and laboriously test the Minnesota Code for classifying electrocardiograms. He also joined in the field activities of the U.S. Railroad Study, and rode the rails west with us.

Project director or co-director from the outset of the Finnish surveys of the Seven Countries Study, and independent investigator of questions within and outside the Seven Countries cohorts, Punsar has made substantive contributions to methodology and to new knowledge of the associations of cardiovascular disease with physical activity, hard water, and blood lipids.

Solid as a rock in the field, reliable in the clinic, genuinely curious and thoughtful in scholarship, Punsar remains unhurried, persistent, and effective. He has contributed a major body of knowledge over a thirty-five-year career, which has strengthened cardiovascular disease epidemiology and prevention, both in Finland and internationally.

After some years of major personal lifestyle changes, including marathon running and stopping smoking, he is now in poor health. To the disappointment of all, he missed the 1993 Seven Countries reunion in Japan.

Esko Orma

Esko Orma was field director for the 1964, five-year follow-up in East and West Finland. A central player and then one of the more brilliant younger Finnish physicians, his curiosity as intense as his personality. He visited the Laboratory of Physiological Hygiene in the Finnish “summer invasion” of 1958, when he, Jaako Kijhlberg, Sven Punsar, and Pentti Rautaharju all came to Minnesota. They established a close working relationship with the Minnesota team, developed new field methods, and carried out sundry personal researches.

Between 1958 and 1964, Orma was a delightful Seven Countries collaborator, full of enthusiasm and bright ideas. Orma and I developed a study together in 1958 in which we used one of the few measures of blood clotting tendency available then – plasma Stypven time, a viper venom enzymic reaction.

We thought cigarette smoking might precipitate thrombosis and sought to compare the chronic and acute effects of smoking on this factor by conducting an experiment in regular smokers among the chronic schizophrenics of the Hastings State Hospital. There are now more direct measures of thrombotic tendency – of fibrinogen, clotting factors, and platelet activity.

At any rate, we had a splendid collaboration in the laboratory and in the field, interrupted only by Orma’s illness in 1964.

The Seven Countries Study: Netherlands

Why Zutphen?

Rural small town Netherlands provided for comparison the intermediate diet pattern of central Europe – reliance on meat, butter fat, and tuberous vegetables, with a minimum of fruits, vegetables, legumes, grains, complex carbohydrates, and fibers. Because only one area was under consideration for study by the Dutch, the rural town of Zutphen, interest was confined to individual correlations of risk and disease. Dutch collaborators have been among the more vigorous to characterize the individual diet, and have conducted frequent, long-term follow-up of their cohort.

I have few adventures-in-the-field to recount, however, from the Zutphen surveys, because Minnesota and other “external” colleagues were not invited by the original principal investigator to participate in the standard baseline, five, and ten-year examinations. The happenings there are nevertheless modestly represented by Daan Kromhout in a companion volume, “The Seven Countries Study: A Scientific Adventure in Cardiovascular Disease Epidemiology.”

Conclusions

Studies among the good burgers of Zutphen have been especially rewarding as a result of the insistence of the independent Netherlands investigators to carry out annual rather than quinquennial surveys of its cohort. This departure from Seven Countries protocol has greatly enriched the data available, particularly on population trends in risk factors, and has enhanced the power of individual prediction from multiple measures of risk characteristics, including diet. The early results of these trends and predictions led the new director, Daan Kromhout, to renovate Seven Countries dietary surveys by reestablishing chemical

analyses of foods to simulate those of the first surveys in many areas. This greatly raised the power of the study for ecologic correlations of diet, risk, and disease.

The Zutphen Study was the first anywhere to find in a population-based sample an association between regular fish consumption and low coronary heart disease risk. It went further, to elaborate the roles of fish and fish oils in cardiovascular disease; the role of dietary fiber in cancer; the inverse relationship of energy intake to coronary heart disease deaths; the association of dietary cholesterol with coronary disease mortality; the inverse relationship of Vitamin C intake to long-term mortality from lung cancer; and the association of sugar and calcium intake with long-term incidence of gall stones.

Repeated measures over the numerous surveys in Zutphen have allowed refinement of the prediction equations from the traditional cardiovascular disease risk factors, as well as of the relationship among skin folds, cigarette smoking and diabetes; the relationship of glucose tolerance to coronary heart disease; the relationship of physical activity to high-density lipoprotein cholesterol; the relationship of energy balance to serum cholesterol; the relationship of alcohol, calcium, and potassium intake to blood pressure; and the intercorrelations of saturated fatty acids, dietary cholesterol, and glucose tolerance.

The Zutphen Study has made major contributions to the methodology of measuring physical activity. The Netherlands group has also extended knowledge of the predictive power of occupation, of subjective feelings of health, and of mental depression, for coronary heart disease and death.

The directions and the productivity of the Seven Countries Study have been importantly affected by the stimulus of the Netherlands group and its principal investigator, Daan Kromhout.

Collaborators

Louise Dalderup and FSP van Buchem

From Ancel Keys' early contacts with distinguished Dutch nutritionists, M.J.L. Dols, P. Muntendam, and C. den Hartog, they were keen to be a part of the Seven Countries Study and named young academic nutritionist Louise Dalderup as the point person. Competent and well organized, Dalderup joined the activity with enthusiasm, participating in the Nicotera pilot survey in 1957. But when the Medical Research Council was finally considering the cost and commitment of joining the Seven Countries Study, they decided that a prestigious senior medical person should be in charge. Professor Van Buchem, recently retired from his position as Chief of Medicine, under a cloud that is not relevant to this story, took over the Zutphen Project with a vengeance. He was resistant to ideas about standardization or to any true collaboration. He allowed no "interference" in the surveys by visitors from Minnesota or elsewhere. Though he frequently created diversions at meetings of the international investigators, we thought that he had eventually signed on to the common study protocol, minus direct quality control or supervision of the field team.

Imagine our surprise, months later in Minnesota, when we received at Stadium Gate 27, the data from the first round Zutphen survey consisting of poor carbon copies of the medical histories and physical forms, and no electrocardiograms. In response to our written and then telegraphic communications, we were informed that the electrocardiograms would not leave Dutch premises, being "too valuable to risk their loss in surface transportation." Air transportation in those days was too costly to be considered. The proposed solution to this standoff: send Blackburn to Holland to read and code the Zutphen electrocardiograms.

Already scheduled for a trip to Venice for the Research Committee of the International Society of

Cardiology, plus a follow-up visit to Geneva to complete the Rose-Blackburn WHO survey manual, I made it a family affair. Wife and kids went to Nelly's parents in Geneva, and I jaunted about the continent on Seven Countries Study business.

Van Buchem's solicitous care of the Zutphen electrocardiograms was so intense that he insisted they be read and coded only in his own study, which in summer was in his beach cottage at Noordwyk. He maintained, furthermore, that I should stay in that somber bourgeois home with him and his wife. I opted rather to stay in a local resort hotel, spending a pleasant eight days there. I read cardiograms for several hours every morning chez van Buchem, to the limit of my concentration, and every afternoon took tennis lessons at the resort's clay courts, and then ran the beach.

The Nordic shore was eerie. My youth on the bright beaches of Florida did not prepare me for the monochrome North Sea beaches, gray sands, puny dunes, chill, steely surf, and scudding dark clouds. The natives bask under an occasional pallid sun behind brightly colored windbreaks, the only color to be seen. Dogs and horses cavort on the sand along with bathers, joggers, and kite flyers.

In the end, all standard requirements of the study, and all eccentricities on both sides, were satisfactorily accommodated and no lasting harm done to the Minnesota-Dutch collaboration. As documented in the companion volume to this, "The Seven Countries Study. An Adventure in Cardiovascular Disease Epidemiology," Daan Kromhout and company – innovative and delightful colleagues – became a central force in the study following van Buchem's retirement.

Daan Kromhout

Kromhout single-handedly instigated a renaissance in the nutritional studies of the Seven Countries Study, bringing to bear his education in nutrition at Wageningen and in epidemiology at Minnesota. He was named principal investigator of the Zutphen Study by Netherlands authorities in 1978, and began participating in the rebirth of Seven Countries Study activities that dated from the Iraklion meeting of investigators in 1979.

Quietly and industriously, Kromhout has effectively exploited the rich data from Zutphen in pioneer investigations of the individual and population correlations of nutrients – particularly fishes, fish oils, and anti-oxidants – with chronic disease mortality.

Representing the second generation of investigators in the Seven Countries Study, he is most appreciated for his innovative concepts and for maintaining excellent collaboration with the original principal investigators. He has renewed, refined, and extended the dietary hypotheses of the study; set into motion effective new investigations and editorial processes; and shared with others a vigorous new leadership throughout the study. Just as the efforts of Hironori Toshima stimulated the study with the remarkable scientific and social conference of 1993 in Fukuoka, so did Kromhout's efforts boost the study with his editorship of the publication, "The Seven Countries Study. A Scientific Adventure in Cardiovascular Disease Epidemiology." Kromhout was the one who initiated the book, obtained funds for its support, and pushed it through to publication in the Netherlands in 1994. He and the Dutch also sponsored a delightful scientific meeting of Seven Countries investigators and others at the 30th anniversary of the Zutphen Study in 1990.

Kromhout remains an active investigator in the Seven Countries Study and of other issues in nutrition. His stature and work have been recognized by his being named Director of Public Health in the National Institute of Health and Environmental Protection in Bilthoven, and by his participation in other international collaborative studies, including MONICA and INTERSALT.

The energy, quiet efficiency, and collegiality of Daan Kromhout is centrally involved in this international study of human characteristics and disease risk.

The Seven Countries Study: U.S.A.

Why The Railroad Study?

The study of U.S. railroad men was the “baby” of Henry Longstreet Taylor. He had the idea to compare coronary heart disease rates among rail occupations to get at the 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.

The U.S. Railway Workers Study was originally designed to be independent from the Seven Countries Study and to make only internal comparisons among rail occupations having different levels of habitual physical activity. It was only later incorporated by Keys and Taylor into Seven Countries analyses to provide representation of the homogeneously high-fat, high-saturated-fat eating pattern of North America. It was not a part of the initial Keys’ hypotheses about differences in coronary disease rates according to habitual diet among contrasting, stable, rural populations.

Lewis Thomas once defined epidemiology as “thumbing through death certificates,” an insensitive and incomplete depiction, at best. But it was such a “thumbing,” done early on and systematically, that revealed to Henry Taylor and those of us who had become his colleagues, that coronary heart disease death rate differences among classes of rail workers were in the direction of the hypothesis that physical activity causes lower rates. Taylor was also the first to criticize his own brainchild, pointing out problems of misclassification of physical activity in the Railroad Retirement Board list of occupations, and of selection bias, which might tend to concentrate workers who were ill, or who were becoming ill, among the less active railroad professions.

This refreshingly candid criticism of one’s own offspring is rarely found in science today. Taylor’s basic integrity was accompanied by a skeptical and dispassionate “Old School Physiology,” which put him in good stead for epidemiological pursuits. So it was that the novel idea was proposed to the National Institutes of Health to examine the active and less active rail workers at their work sites, measuring coronary disease incidence in the railway cohort while accounting for measured confounders and coexisting morbidity. To his 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 U.S. Railway Workers Study.

Fall, 1957 – Riding the Rails

The Railroad Study operation was “first class” from the beginning, and I was happy to be involved. I had a few pangs of regret when I was unable to accompany Ancel Keys in the fall of 1957 to conduct pilot surveys in Finland, Crete, and Southern Italy, but my services were needed to get the Railroad Study on track. This we did, with procedures, forms, and the beginnings of cardiovascular disease classifications that would eventually become The Minnesota Code and the WHO book: Cardiovascular Survey Methods.

In those exciting early days, I particularly enjoyed working with Taylor to design a unique traveling laboratory. He proved extremely skillful in face-to-face negotiations with railway managers and union brotherhoods, obtaining, among other things, the long-term loan of a Pullman car for the study. With the new National Heart Institute grant, he proceeded to have that car renovated in the old Great Northern maintenance yards off Como Avenue in St. Paul, 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, medical history, physical exam, and blood pressure; and a large work area for the resting and exercise electrocardiogram. Toward the end, there was a booth for the chest x-ray and then a wet lab area for blood and urine sample processing.

After a trial run in the old St. Paul Depot, we moved out on the rails, hooking up to the power, water, and steam in stations or rail yards across the line, northwest to the cities of Spokane, Pasco, Seattle, then down to Portland and San Francisco, and back again.

Taylor had carefully negotiated two essential elements for the success of the study: Clerks could be examined at their work site during working hours without their pay being docked, and, at my insistence, information we collected on all employees would be held confidential and not provided to railway physicians or companies. These guarantees clinched the enlistment of the rail brotherhoods. The first-round survey involved comparing the risk factors and medical findings of rail executives and clerks with switchmen and right-of-way personnel, among whom Taylor's pilot work had validated different levels of habitual activity and on-the-job oxygen consumption.

The rail men were a jovial bunch, and our crew, too, was congenial, working together effectively and examining up to forty men a day. Our team developed in this first-round survey 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 definition of the population with a census; intensive recruitment; thoughtful scheduling; and central data-editing, processing, and analysis. In our working and traveling together, we also elaborated – by plan and by trial and error – much of the general field procedure that the Laboratory of Physiological Hygiene, and then the Division of Epidemiology, utilized in subsequent operations.

We learned, for example, that staff, after six straight days of work, needs a break in order to remain effective. And after three weeks straight, they need a brief home leave. We also found it impossible to use a converted 1895 Rock Island Line presidential sleeping car as a dormitory. So we were housed in quiet motels and ate dinner in attractive restaurants. This helped relieve the heavy work routine and maintain morale over the long haul. We also learned to avoid over-booking, particularly the first day at a new location.

There were many delightful adventures “on the rails,” both intellectual and social. As we traversed the land, we on the team held long conversations about the colorful rail men we met, and about the burgeoning new field in which we were involved – cardiovascular disease epidemiology. On the second round of exams, starting in 1962, I had my soprano saxophone along. I'd serenade 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 we made contacts to hire and train short-term medical examiners. Several Twin Cities colleagues, Robert Rothenberg, Dennis Kane, James Dahl, “Mack” Richards, and William Moore, participated in two survey rounds over six years, '57-'58 and '62-'63. We were joined by a series of overseas visitors who came to train at the new “epidemiological Mecca” at the University of Minnesota, Stadium Gate 27.

The staffing was quite exceptional as we began the first-round survey, with such Minnesota experts as Francisco (Paco) Grande helping with the initial dietary interviews, and Joseph (Jaschka) Brozek doing the anthropometric measurements. I, along with technicians Walt Carlson and John Vilandre, and later, biophysicist Pentti Rautaharju, carried out the exercise electrocardiographic monitoring. Nedra Foster and Gail Dolliff handled the blood, urine, and x-ray technical duties, while I conducted the clinical exams, along with drop-in colleagues. In all it was a happy, disciplined, and effective operation.

We chose to study U.S. Railroad employees because they were largely stable in their specific occupations and in their lifetime employment, and had measured differences in the physical activity required at work. Moreover, all rail employees are covered by a pension plan, which maintains detailed employee records of employment, disability, retirement, and death. Permission was required of the rail companies, of the Railroad Retirement Board, and of the various labor unions involved, including each local railroad brotherhood official. All twenty rail companies that operated in the northwestern quadrant of the United States – circumscribed by Chicago, St. Louis, San Francisco, and the Canadian border – were involved. Selection of thirty sampling units ensured proportional representation in each geographical area and each size of urban area. Our staff, usually Taylor or me, recruited and scheduled participants at union meetings. The laboratory car visited each location at least twice during each survey round. Unfortunately, I kept no written or photographic record of the details of these railroad expeditions.

Conclusions

We learned from the Railroad Study that it is difficult to make valid occupational comparisons of cardiovascular disease rates when so much depends on the characteristics at entry and reasons for going into the occupation. Subsequently, there is selection tending to concentrate coronary events among the less active jobs. We also learned “the hard way,” that the numbers of men sampled were inadequate for a valid comparison of active and inactive populations, and that 10,000 to 15,000 men would have been required in each activity class, based on five-year coronary heart disease incidence in the sedentary group, to demonstrate any real differences related to job activity.

The Railroad Study was among the first major longitudinal studies in which an independent relationship was not found between relative body weight or skin fold obesity and risk of coronary heart disease. On the other hand, the study did confirm very early the universality of the “standard” coronary heart disease risk factors, thus contributing to the strong inference of their causal role. Data from the study were entered into the American Heart Association Pooling Project, the first statistical summary carried out in cardiovascular disease epidemiology.

We also studied the occupational differences in reported mortality rates for the entire railway population. The relative risk of death from coronary heart disease for sedentary versus active railroad populations nationwide was 1.18. We may conclude that the relative risk ratio of 1.18 for deaths between clerks and switchmen is perhaps the best estimate available of the true difference in coronary heart disease incidence between sedentary and more active rail occupations (which have an average 600 kilocalories difference in physical activity per day). This can be compared to risk ratios of 2.2 for high blood cholesterol level, 2.1 for systolic blood pressure, 0.95 for relative weight, 1.2 for skin fold thickness, and 1.3 for height.

The Railroad Study, along with the experience in Finland, has led us to conclude that, within high-risk cultures, skin fold obesity, relative weight, and physical inactivity are coronary heart disease risk factors for the individual of “a second order of magnitude.”

Finally, it should be recalled that the Railroad Study was developed by Henry Taylor independently of the Seven Countries Study and was only much later co-opted into the larger organization and analyses. Despite the industrial nature of the railroad population, the Railroad Study strengthened the comparative framework of Seven Countries by adding an affluent industrial culture. And what was learned on the rails about field methods, data handling, and disease classifications was directly applied to the overseas and general operation of the Seven Countries Study, beginning in the fall of 1958.

Collaborators

Louise Dalderup and FSP van Buchem

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The Seven Countries Study: Japan

Why Japan?

Ancel Keys and colleagues hypothesized that the Japanese, at the lower pole of fat diets, would hinge the correlation between saturated-fatty- acid intake and coronary disease risk.

In the 1950s, a few things were clear about Japan’s traditional diet even

before the Seven Countries Study or modern nutritional surveys. It was extremely low in animal fats, modest in protein, relatively high in fish, and high in complex carbohydrates. The Japanese diet also contained several times more salt than most other traditional diets.

The early hypotheses of our Japanese colleagues about the causal role for hemorrhagic stroke of low-fat, low-protein diets, with attendant low blood cholesterol levels, were hopelessly confounded by the high-salt, high-blood pressure picture.



Even now, in the 1990s, Japanese investigators attribute, without the evidence needed, the decline in deaths from cerebral hemorrhage as much to the rising average cholesterol levels as to the lowered average blood pressure in Japan. The finding of excess risk of cerebral hemorrhage among individuals with low blood cholesterol values in other cultures where diets are not high in salt has, however, provided strength to their views.

At any rate, the very low-fat diet set the stage for Keys to include Japan in the Seven Countries Studies, thanks to early studies by Noboru Kimura, and independently, by Yoshio Komachi, a distinguished epidemiological colleague.

A pilot study by Keys and Kimura showed differences in blood cholesterol level among miners, clerical workers, and executives within Japan. It also found striking differences in beta-lipoprotein cholesterol levels between Japanese on the mainland and in southern California, while alpha-lipoprotein levels were comparable.

Kimura, mainly interested in the internal differences in Japan, chose the farming village of Tanushimaru to contrast with the predominantly fishing village of Ushibuka because of theories about fish and protein intake being protective against cerebrovascular disease.

Tanushimaru, Third Round, March, 1968

As in the farming villages of the Mediterranean regions, surveys in Tanushimaru required that we arrive in the field immediately before planting or after the harvest, to be assured of local cooperation. So, the Tanushimaru survey was geared up in March, with one drizzly, somber day strung out after another. It was particularly damp in the Kurume hotel where I was preparing for the field by reviewing forms, schedules, and procedures with Toshima.

In Tanushimaru, we had the full program of automated exercise electrocardiograms, chest recordings, respirograms, and pulmonary flow curves recorded by Rautaharju's team, and a marvelous local team of smiling, industrious, young Japanese physicians and nurses, somehow liberated from their regular jobs for several weeks.

We examined all farmers of the Tanushimaru region, with close to a hundred percent response rate. The major logistic problem was the damp cold. I did a lot of talking, encouraging, and walking about the center to

ensure that the coal grates and the kerosene stoves were appropriately distributed so that men awaiting physical examinations and blood pressure measurement weren't exposed to cold stress. I probably needn't have worried. Those hardy, wiry men were well adapted to the climate.

The only other hazard I knew of in Tanushimaru was the catered team lunches that arrived in festive, lacquered boxes containing bamboo trays of sundry unidentifiable squares, rounds, and triangles; colored fish paste; cold clots of rice wrapped in dark, paper-thin seaweed; briny pickled fruits and vegetables; and semi-cooked mussels and shrimp. I chose to eat the rice only, using chop sticks, much to the amusement of our Japanese colleagues, washing it down with Kirin beer. This allowed me to survive until dinner, when I could have bland dishes of tempura or sukiyaki.

Another hazard I had heard about but not experienced: Japanese earthquakes. That was quick to change. The team was hard at work one morning in the frame elementary schoolhouse of Tanushimaru, counting pulses and taking blood pressures, while I supervised exercise tests. Suddenly, I felt as if something were disturbing my balance. Looking out the window at a stone memorial to the founder of the school, three stones, one on top of the other, were dancing, undulating but not falling. The school's flimsy wood and bamboo floors and walls were creaking wildly.

The survey activity paused, the Westerners looking at one other in consternation, the Japanese poised calmly at their posts. The undulations continued for a good ten seconds, subsided, started again slightly for a couple of seconds, and then disappeared. I understood then the reasons for the light architecture. A masonry building would have crumbled and fallen on us. Afterwards came the "rush," typical when one has escaped danger.

Relationships were particularly cordial with Yasume Egami, the family practitioner of Tanushimaru. One of our sample cohort, he visited the survey center daily to chat with the participants. He knew all of them, as well as their families and family histories. His blessing raised our credibility above that of the distant academics we might otherwise have been considered. I chatted with this kind man on his visits, enough to learn of his sensitivity, intelligence, and understanding of what we were doing. His devotion to his community was clear.

The one time I visited Egami's home and commented on its beauty, he must have seen my eyes rest momentarily on a particularly handsome lacquer. Imagine my chagrin when, on the train north to Tokyo, I opened the package he had placed in my arms at the station. There was the lacquer, a deep Chinese red, emblazoned with a gilt lion.

Twenty-five years later, that lacquer decorates a Japanese corner of my home. Imagine my greater embarrassment when I learned indirectly some time later that the lacquer had been handed down to him from his great grandparents. I, the visiting Westerner, have his precious family heirloom.

I have not yet learned – and expect will never learn – how to deal with such generosity, or with the social debt that it incurs. But I have learned to avoid expressing any admiration of the belongings of the Japanese!

Ushibuka, Third Round, October, 1970

Ushibuka, the southernmost village on Kyushu, which is the southernmost island of Japan, was chosen by our Japanese colleagues as representative of a stable, rural culture predominantly of fisherman. It would

serve as contrast to Tanushimaru, the farming community in the interior.

The fishermen of Ushibuka are a hardy lot, often at sea for as many as nine months of the year, their catch bought on the high seas by following fish tenders. We were advised that in October, a blustery cold month in the China Sea, most fishermen were home on leave with their families.

Arriving at Ushibuka by boat from Minimata across the bay, we were met by the local physician, Toseio Fukomoto, who spoke no English. His gestures and wonderfully kind face nevertheless helped us feel at home. He explained to me through a pleasant translator, his hospital nurse, that I would be living in the hospital and eating at his house.

I felt grand, as do all Westerners, in the presence of such kindness. It only proves unfortunate when we come to accept this hospitality as our due. The translator told me, aside, "I think I've heard, Professor Blackburn, that in addition to Dr. Fukomoto's usual household chef, he has laid on two assistant chefs for your visit!"

This concerned me. I had neglected to ask my Japanese academic colleagues, Toshima and Kimura, to prepare the way for me, as other colleagues in the Seven Countries around the world had figured out how to do long ago. I was neither "culinarily curious" nor "gregoriously gourmet." I realized that I was trapped. For the successful conduct of our study in Japan, I would have to submit to Ushibuka hospitality in every regard.

Prior to arriving at the good doctor's home for our first dinner together, I took a stroll around the bay to look at the fishing boats tied up at the wharf and to see the cargos they had brought home for local markets. Exotic scenes and tantalizing aromas ranged from fishes to hawsers to the straw that packs the ice in the ships' holds, to tea, spices, and seaweed.

Stronger than these delights was the sickening odor of sewage. Nevertheless, the waters of the harbor were clear. I could see echinoderms, starfish and spiny sea urchins, fixed to the rocks below. But I knew the clarity of the water was misleading.

Far across the bay, we could see the peninsula of Minimata. Life magazine had just a few years earlier depicted on its cover a young woman victim of Minimata Disease – chronic mercury poisoning. Industrial toxins drained into the bay, built up in the food chain, and concentrated in the fish and seafood consumed so prominently by the Japanese. The taught skin around the victim's face; the drooling mouth; the scrawny, contracted limbs and distorted posture, forever fixed, worldwide, the image of industrial pollution.

West of Ushibuka Harbor, one could see the tiny island where the Portuguese established a trading foothold in 1600, built a church, and converted many islanders to Christianity. The church still stands as a memorial to the courage of those Japanese who, later, when the Portuguese were driven away, were challenged by their Samurai leader to stand on the symbol of Christ and swear they were not Christians. None of these devout new converts, according to legend, could desecrate the symbol. They all admitted their religious conviction and were carried off to their deaths.

Beyond the island, I watched the sun set over the Japan Sea, with red, purple, and lavender-scalloped clouds radiating in long tendrils, like some huge sea animal. The cries of sea birds, the beauty, and the centuries of tradition – all were inconsistent with my image of Minimata Disease and with the pervasive stench of Ushibuka Bay.

New Hazards in the Field: Sashimi

One hour later, a parboiled, pink, Western creature emerged from the 120-degree waters of Fukomoto's Japanese bath, clad in a lightly starched yukata (lounging robe), and feeling every bit the honored visiting American. We sat down together – Kimura, Toshima, Fukomoto and I – and the dinner service began. Fortunately for me, Fukomoto had a dining area allowing our feet to be placed comfortably on wooden racks below the table, so I didn't have to sit cross-legged. From the racks, a soft heat radiated, to take away the chill of a wintry day in the otherwise unheated house.

With fanfare, the rice-paper partitions opened and three impeccably clad chefs entered and laid before us the first course – purple, spiny sea urchins like those I had seen a short time before at the bottom of smelly Ushibuka Bay. Their tentacles were still moving. I was instructed to use a tiny spoon to dip into the shell of the living urchin and extract an orange granular substance, presumably the roe, and to transfer this mass to a small enamelware dish. This I was to mix with a spiced, highly salted seasoning, and eat. The delicacy was meant to prepare the palate for later courses.

Down it went. The first wave of nausea and apprehension swept over me. I tried to convince myself that my discomfort was psychological – that the chances of becoming ill, from an allergic or toxic reaction to the seafood or later from contaminants – were extremely remote. I should simply face the odds and take it like a man!

The second course arrived, presumably from the same foul bay. It was the largest lobster I have ever seen, resembling the Florida species without major claws but antennae well over a foot long. The head chef, in a deft motion with an incredibly sharp blade, sliced open the cartilaginous carapace and, with a simple gesture, pried and propped it open, exposing the jelly-like, translucent, uncooked flesh.

I assumed that lobster process sewage actively, not like oysters and clams, and that its meat was not likely to contain the source of pollution I had smelled. But having avoided sashimi so far, and having never before eaten a piece of raw fish or seafood, I felt overwhelmingly threatened. At the first bite, I broke out in a sweat, convinced that I was having a reaction. The lovely pink glow from the hot bath merged into a ghastly pallor.

Just at that moment, the nurse serving as my translator entered the dining room with effusive apologies and numerous curtsies, and knelt between my host and me. She explained to me, systematically, the dishes served and those coming up. Fortunately, subsequent dishes were baked or boiled. I made it through the meal without embarrassing myself, eventually retiring to my room in the hospital, where I did as much as I could to lose the exotic meal I had consumed.

The next morning, summoning the translator, I started with the long story of how, years before in Yugoslavia, I had become ill with Shigellosis, a form of typhoid, and had lost both good digestion and all lactose tolerance as a result of the severe dysentery.

I indicated that for survival I had been forced, over subsequent years, to bring much of my own food on field studies. I pleaded that I could eat only well-cooked, lightly seasoned fish, meat, and vegetables, with a little of the local beer or wine, and lots of rice. I explained earnestly that I understood the remarkable sacrifice my host had made to provide this hospitality. But I explained to her, as I could not explain to him directly, that unless he wanted me as a long-term patient in his hospital, a radical shift in the menu was

indicated. I needed simple fare – vegetable or seafood tempura, or sukiyaki, boiled meats and vegetables.

The good doctor, whether or not he ever really understood, “got the message.” He fired the two extra chefs and put on alternating meals of tempura and sukiyaki, along with desserts of canned Bartlett pears. This change allowed me a hard-working and delightful sojourn of several weeks on the southern island of Japan.

The Ushibuka survey concluded, the entire survey team stood in a row at the quai, waving to me at the rail of the ship. Long confetti streamers led from my heavy pink hands down to the delicate olive hands of our hosts on the wharf. I flirted with them by tugging various lines of confetti until the connected one giggled. Later I found in my stateroom the ultimate gift from Fukomoto: a new Seiko quartz watch!

Thirty-fifth Anniversary Conference of the Seven Countries Study, Fukuoka, October, 30, 1993

The Seven Countries Anniversary celebration arranged by Toshima and Koga was professionally and socially delightful, particularly the renewal of old friendships. Flaminio Fidanza refound his old “moniker” for me: “Enrico Il Nero,” in contrast to Henry Taylor whom he called “Enrico Il Grande.”

The scientific part of this celebration dealt mainly with the changes observed by the Seven Countries investigators in the lifestyles and disease experience of their regions over the decades since the original surveys. These changes are touched on in the several conclusions throughout this presentation and are treated in detail in a companion volume, *Lessons for Science from the Seven Countries Study* (Eds. H. Toshima, H. Koga, and H. Blackburn, Springer Verlag, Tokyo, 1995).

The social part of the conference honored Ancel Keys, approaching his ninetieth birthday. It included numerous post-prandial reminiscences by the Seven Countries colleagues. A few of these are reproduced here.

Srejko Nedeljkovic tells of life in Belgrade these days – many burglaries, and a large black market run by thugs. The whole of society is in upheaval in the former Yugoslavia. He felt fortunate to have made the trip, “escaping” through Budapest.

Alessandro Menotti reminisces about one of the Italian surveys: “In the mornings between 9:30 and 10:30 the electrocardiograms were terrible because of AC interference. After three days of this, we discovered that in the basement of our building was a kitchen. At that moment each day, the cook started an enormous potato-peeling machine, and the electrical fields created were disturbing the ECG recording. We had to call back the men who had been seen during those hours, because their records weren’t readable at all by the Minnesota Code!”

“Another story started at the survey in Rome for the Italian Railroad Study. Our major consultant was Henry Taylor. In my family, he was called, “the American cowboy,” because of his kind of casual fooling around. He stayed in a small pension. Every morning, I went to pick him up by car to take him to the hospital where the work was going on. During this period his wife was traveling in Denmark. She bought a new Volvo to take to the States, and drove it down to Rome. There the car was available to Henry Taylor, so one day I didn’t have to go to take him to the hospital.

On that day, he didn’t arrive for several hours. I called the pension to find out what happened. At the first

bend, a curve to the right, he had crashed into the first car parked on the street. He had a lot of problems with insurance, and he didn't speak Italian. But the Volvo resisted very well; they are very strong cars. The next day, again, he didn't arrive. Again, he had crashed into another car at the same curve, at exactly the same place! The telephone calls for the insurance posed all kinds of problems. The third day, the same story. So I started picking him up again.

At the end of the survey, together with his wife (she drove), they took the Volvo to Rotterdam. They put the car on a ship and took a plane back to Minneapolis. There they waited for the ship to arrive in New York so they could pick up the car. Unfortunately, the ship sank in mid-Atlantic!"

Andy Dontas also reminisces. "In 1956, at a meeting of the American Heart Association in Chicago, Ancel Keys was already expounding his ideas about diet and heart disease. I approached him afterwards as I was about ready to return to Greece, and we had a long talk about possibilities for field research."

"You can't imagine the problems we had to face in the Crete pilot survey in 1957. It was just like going today to Nigeria or maybe to Nepal to do a study. Electricity was a big problem. No electricity anywhere on Crete except in Iraklion. There was no running water. There were no paved roads anywhere except in Iraklion.

In Corfu the next year the difficulties were more personal than physical because no participant could be convinced to be examined unless he got some kind of reward. So we had to examine his family as well, and do their electrocardiograms and everything, free of charge.

I think the best story of the Crete survey was when we walked down to the dock area where all the nice grapes were packed. Flaminio Fidanza was worrying all day how to pack the grapes he had bought, and so finally put them in his bathtub.

He was rooming with Kimura, who complained bitterly. One wanted to eat, the other to bathe! The prototypical Italian and Japanese."

Conclusions

The Japanese cohorts share with the Greek Islands the lowest coronary heart disease risk of the Seven Countries, hinging the lower end of the regression line between risk variables and coronary heart disease incidence. The Japanese had the lowest fat and lowest saturated fatty acid dietary intake, and the lowest average serum cholesterol level. Despite a steep age rise in average blood pressure and widely prevalent cigarette smoking, the Japanese had the lowest coronary disease rates.

The paradox is that their stroke rate is relatively higher than would be predicted by the Japanese configuration of blood pressure and other risk factors. This has led to the wider observation of a high prevalence of hypertension in other countries where there is the same high-salt, high-carbohydrate, low-fat, and low-protein traditional eating pattern.

The findings in Japan have clarified the remarkable differences in population causes of the two major forms of stroke – brain infarction and atherosclerosis, and cerebral hemorrhage and hypertension. They have led also to an intensive re-examination of the causal versus confounding aspects of low blood cholesterol levels found in those who subsequently die of hemorrhagic stroke and non-cardiovascular disease deaths.

These associations have now been extensively confirmed outside Japan.

Most remarkable in the Japanese cohorts has been a dramatic change in risk characteristics over twenty years: a more than doubling of those with body mass index greater than twenty-six; a more than doubling in the sum of skin folds; an increase followed since 1982 by a decrease in prevalence of hypertension; and a twenty-five percent increase in average serum cholesterol levels. All these are associated with a departure from the traditional Japanese diet and the significant automation of farming. There have been remarkable increases in protein intake – from eleven percent to sixteen percent – and in fat intake – from ten percent to twenty-two percent of daily calories.

These lifestyle and risk factor changes have been associated with a precipitous decline in hemorrhage stroke deaths – from about 4 per 1,000 per year to 0.3 per 1,000 per year, and generally attributed to Westernization of the eating pattern, while coronary disease mortality has not shown a significant increase in Japan. Our current hypotheses of the major population causes of coronary heart disease predict that an epidemic will arise when a threshold of mass exposure is reached and maintained for a decade or so, with average serum cholesterol levels above 200 mg./dl. This should come about soon, if current trends continue in Japan.

But meanwhile, Japan has among the lowest cardiovascular and non-cardiovascular death rates, and the highest average life expectancy in the industrial world. Continued close surveillance is advisable, however, because of the increasing intake of saturated fatty acids and the continued high level of cigarette smoking. In fact, programs to prevent high risk in the first place are clearly indicated (WHO's "primordial prevention"). Certainly countries in rapid transition, particularly industrial nations such as Japan, present a fruitful opportunity for epidemiological research and for policy and programs in prevention of high risk in the first place.

Noboru Kimura

Noboru Kimura was one of the first clinical scientists anywhere to highlight the rarity of coronary disease and frequency of hemorrhagic stroke in Japan and to pose hypotheses about their causes. He was also one of the first clinicians anywhere to look beyond the clinic to the general population for the causes and prevention of common cardiovascular diseases.

He sought out Ancel Keys in the early 1950s to encourage him to come with Paul Dudley White to Japan and make both internal and external comparisons of cardiovascular disease rates. And he sat as one of the pioneers, with Paul White, Gunnar Björk of Sweden, and Ancel Keys, on the platform of the first major symposium on cardiovascular disease epidemiology and prevention at the World Congress of Cardiology in Washington, in 1954.

Our friend and colleague, Kimura, embodied all the strong traits we think of in traditional Japanese culture. "Nobe," as his American friends called him, was blessed with a remarkable serenity and good humor, a quiet sense of values promoted by example rather than pedantry, a prodigious industry disguised by calm efficiency, an effective authority without authoritarianism, and a lifetime loyalty to friends.

Not only innovative on his own, but sensitive to innovations elsewhere, he came for a six-month period in our laboratory in 1952, at the very time that Ancel Keys was beginning to formulate ideas about the importance of lifestyle in population disease differences. In further meetings with Keys, at the World Congress in Washington in 1954 and at the WHO Expert Committee Meeting in Geneva in 1955, their discussions about collaboration continued.

Both recognized that Japan held a key to understanding the mechanisms of mass atherosclerosis. Kimura sponsored the formal meeting with Keys and White in Fukuoka in 1956, when they set up the first study to demonstrate occupational differences in cardiovascular disease risk in Japan.

Kimura became a regular fixture in all Seven Countries Study activities, present at the pilot studies in Italy and Crete in 1957, and at the first survey in Makarska in 1958. After Makarska, he immediately launched the Japanese surveys in Tanushimaru and Ushibuka. He became principal investigator and field director for all Japanese Seven Countries activities thereafter.

The solid collaboration and collegiality of Noboru Kimura, and the findings of the Japanese surveys, have contributed to the useful outcomes and understandings of the Seven Countries Study and to the scientific, professional, and personal satisfactions of his study colleagues.

Collaborators

Hironori Toshima

In the early 1950s, “Hiro” Toshima trained with Kimura and then in the early 1960s took a post-doctoral fellowship at the Laboratory of Physiological Hygiene in Minnesota. At Minnesota, he worked primarily in electrocardiography, but was exposed to the epidemiological pursuits going on there. He later took on the study leadership in Japan after the retirement of Kimura.

Toshima reinvigorated the Japanese Seven Countries Study by recommencing surveys in 1977-78 with a newly established cohort representative of that period, twenty years following the baseline survey. He broadened the age range and included men and women in this survey, as well as adding new risk measurements.

In addition to carrying on the professional and personal traditions of Kimura, Toshima has been innovative in cardiovascular medicine in Japan and internationally. For example, he helped introduce modern cardiac rehabilitation strategies in Japan. Toshima is now Director of the Kimura Memorial Heart Foundation, which is concerned with primary prevention and health promotion.

Closest to the hearts of his international colleagues was the great personal effort, and the immense contribution Toshima made in bringing together all the Seven Countries principal investigators to celebrate the thirty-fifth anniversary of the study, along with the ninetieth birthday of its founder, Ancel Keys. This took place in a superb professional meeting and social occasion in Fukuoka on October 30, 1993, documented in a publication, “Lessons for Science from the Seven Countries Study.”

The Seven Countries Study: Addendum

The University of Minnesota Laboratory of Physiological Hygiene, located at Memorial Stadium Gate 27, on the Minneapolis campus, was at the hub of the Seven Countries Study operation from the outset.

The research of Keys and collaborators had grown rapidly during World War II. The small faculty of the laboratory traded the teaching of physiology to physical education students for the space of the visiting coaches' locker rooms underneath the bleachers of the stadium.

There, researches on the biology of human starvation, which became classics, were carried out. Over the years, the underground facility expanded steadily, eventually occupying the entire south wing of the stadium. Those who trained and visited there still look back with great nostalgia on the scientific activity and collegiality in that unique setting. The work on human biology, and on the population phenomena causing mass diseases, was satisfying for all participants, a different satisfaction perhaps from those of other subterranean researches (eg. Enrico Fermi's atomic facility located under the University of Chicago stadium!)

Gate 27 housed the coordinating staff of the Seven Countries Study and the principal offices of Ancel Keys, Henry Taylor and me. It also housed the Seven Countries chemistry and nutrition laboratories; the data editing, analysis and statistical center; and was the site of ongoing researches and training of Seven Countries collaborators from around the world. These activities are described in greater detail in another volume, *The Seven Countries Study: A Scientific Adventure in Cardiovascular Disease Epidemiology*.

In 1967, Alessandro Menotti took over in large part the Seven Countries coordination responsibilities, following his training at the London School of Hygiene and at the University of Minnesota. Since his 1993 retirement, the coordination is shared between the University of Minnesota and the National Institute of Public Health in The Netherlands. Menotti remains a part-time professor at Minnesota.

At the outset of the Seven Countries Study, a firm collaboration in methods development grew between us and Geoffrey Rose at the London School of Hygiene and Tropical Medicine. We wrote together a manual embracing all cardiovascular disease survey methods under the aegis of the World Health Organization. The Third Edition of that manual, *Cardiovascular Survey Methods*, is in preparation under the chairmanship of Russell Luepker, now head of the Division of Epidemiology at the School of Public Health in Minnesota.

Here I recount the development of the Minnesota Code, which was a part of our central preparations for the Seven Countries Study.

- For more about Gate 27 and the work that went on there, download a copy of, "Behind Gate 27 In the bowels of the University of Minnesota's Memorial Stadium, Ancel Keys launched seminal studies on starvation and heart disease."