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Cardiovascular disease epidemiology

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Personal experiences

I arrived at cardiovascular disease (CVD) epidemiology from an early interest in electrocardiography as a medical student under George Burch at Tulane in the late 1940s. Later, I did a Masters thesis at Minnesota with Ernst Simonson and Otto Schmitt on the 'spatially corrected' QRS interval. It was pedestrian research but good training in careful measurement, repeat variability, defining the 'normal', simple statistical analysis, and practical aspects of survey methods.

This thesis work, carried out in the intensely searching atmosphere of physiologist Ancel Keys' Laboratory of Physiological Hygiene, came at a romantic time in the early history of CVD epidemiology, when Keys had become a 'medical Marco Polo'. From travels about the world with Paul Dudley White, the international 'dean of cardiology', he would return to Minnesota with bountiful news and hypotheses about cultural differences in the frequency of heart attacks. The Holy Grail lay, he suspected, in the diet and 'mode of life' of populations living varieties of traditional lifestyles.

Several things in Keys' vision rang true from my experience. In the summer of 1949 in eastern Cuba I had discovered the severe limitations of medicine to cope with mass diseases due mainly to poverty and ignorance. These were matters for public health and the political economy, quite beyond the meagre efforts of medical missionaries.

That first view of the sociocultural origins of common diseases was confirmed while I was serving as public health officer for the US Displaced Persons Program in the camps of Austria and Germany from 1950 to 1953. From these exposures I was primed, when the opportunity arose, for a career in public health and for a 'population view' of epidemic cardiovascular diseases.

Ancel Keys' 1956 invitation to become a research associate in 'The Lab' and project officer for the cross-cultural Seven Countries Study of cardiovascular diseases, offered an international career exploring a major phenomenon of public health and involving my early interests and experience. It was too attractive to refuse, despite its paltry stipend.

Keys' direct challenge to me—to render the clinical components of cardiac diagnosis sufficiently unambiguous, quantitative, valid, and reliable for comparative field surveys of CVD—I found feasible and even 'right down my alley'. It led to early signature publications: 'The electrocardiogram in population studies' (the Minnesota Code), and, with Geoffrey Rose, the WHO manual, *Cardiovascular survey methods*.

The same day as Keys' invitation, I received the offer of a junior faculty position in the medical school. I soon learned from its annoyed chief of medicine that my signing on with Ancel Keys and 'those weird people doing those crazy things under Gate 27 of the football stadium', would almost certainly exclude me from the academic elite of internal medicine!

So be it. Interesting and important things, including the birth of cardiovascular disease epidemiology, were under way at Minnesota and abroad.

Introduction

Recognition of epidemic heart attack in the mid-twentieth century, with attempts by pioneers to explain and reduce its burden, provides lessons and drama unparalleled in chronic

disease epidemiology. At that historic moment, several streams of knowledge and circumstance converged to provoke formal epidemiological study:

◆ Cardiovascular experts were making advances in cardiac diagnosis and in the understanding of atherosclerosis and hypertension, two processes fundamental to the cardiovascular disease (CVD) epidemic.

◆ Observers of trends in CVD deaths before, during, and just after the Second World War proposed arguments that these trends were real and that the abrupt decline in CVD deaths in Europe was due to wartime changes in nutrition.

◆ Others, returning from travels, brought back tales about large differences in the frequency of heart attack, along with hypotheses about the cultural origins of those differences.

A few pioneers in the trenches, mainly experts in cardiovascular fields and most without epidemiological training, integrated evidence from these several sources. They posed critical questions about the possible causes of CVD and undertook studies in populations, creating a new field in what would become the broader epidemiology of non-communicable diseases.

The creation was no 'Big Bang', but it did occur abruptly—around 1948—and the universe expanded rapidly. Independent beginnings in several centres internationally coincided with a deliberate effort by the US Public Health Service in which the Framingham Heart Study was initiated (Dawber 1980; Oppenheimer 2005). This designated 'moment of creation', 1948, saw the start of formal prospective epidemiological research into possible causes of CVD among healthy cohorts, beginning in Minnesota and in Framingham.

That early period also saw the founding of bodies critically supportive of this 'new' kind of research: the World Health Organization (WHO), the US National Heart Institute (NHI), and the American Heart Association (AHA), which had just reorganized into a public agency. Coincident with these activities were new directions in research and training at the London School of Hygiene and Tropical Medicine and soon thereafter in numerous centres worldwide (Morris 1957).

Origins: pre-1948

A small coterie of CVD experts recognized heart attack as epidemic among several industrialized countries in the years just before and after the Second World War, predominantly among men from upper economic classes and in their prime years. Heart attack was even popularly called 'executive disease'. A few leaders turned their curiosity about the causes of the epidemic to the community and culture from which the many cases derived.

The state of medical ignorance and cautious attitudes about the possible environmental influences on CVD *circa* 1948 can hardly be appreciated today. Hypertension was known to have a direct relation to heart failure and to stroke but its connection with heart attack was not clear, and at any rate there was little to be done about it. Vascular diseases generally were relegated to 'an inevitable consequence of aging'. The importance of 'cholesterol', long known as a main component of arterial plaque and a cause of experimental dietary atherosclerosis, was for many years 'pooh-poohed', along with habitual diet, as 'a simplistic causal view of something as complex as atherosclerosis' (Jeremy Swan, personal communication, early 1970s). Smoking and obesity were merely distasteful; physical activity was dangerous and unfashionable; 'stress' and heredity were fundamental but inescapable.

'Be wise. Reduce your weight', was about as far as preventive practice went in the late 1940s. Research was informal, clinical, and privately funded. And public health recommendations to avoid risk were nowhere to be seen.

Pathology

The initiative of Ignatowski and Anitschkow, pathologists in the Russian Imperial Medical Institute, led to the modern understanding of atherosclerosis as the anlage of epidemic CVD. In the early twentieth century, they hypothesized that a 'rich' diet was responsible for accelerated aging and atherosclerosis. In those flourishing days for experimental pathology, they fed human diets to rabbits, producing fatty arterial lesions resembling those of human disease. Anitschkow determined that dietary lipids and cholesterol, rather than protein as Ignatowski postulated, were the arterial pathogen. His classic review of experimental atherosclerosis, in Cowdry's popular text of the 1930s, anticipated virtually every issue about atherogenesis explored since that time, including regression of atheroma (Anitschkow 1933).

Anitschkow's findings and syntheses were widely disseminated, stimulating much clinical-pathological study and causal ideation (McGill 1968).

Diagnosis

At the turn of the twentieth century, Wilhelm Einthoven of Leiden developed the string galvanometer electrocardiograph, which vastly facilitated cardiological diagnosis, particularly after its clinical application by the British investigator, Thomas Lewis (Einthoven 1903). Paul White came to study with Lewis in the 1920s and, with others, brought the apparatus and the art of electrocardiology back to the USA.

Some years later, Herrick's description of myocardial infarction with survival is generally given priority in Western medicine for establishing the syndrome of clinical and electrocardiographic manifestations (Herrick 1912; White 1948). The electrocardiogram became the major diagnostic tool in early clinical and epidemiological studies of coronary heart disease.

Stroke, on the other hand, was properly diagnosed much earlier, though it was only with development of brain imaging in the 1970s that its origins were successfully differentiated, during life, as thrombotic, embolic, or haemorrhagic.

Wartime mortality fluctuations

The rise of CVD mortality during the first half of the twentieth century was recognized early by a few experts internationally, including Joseph Mountin of the US Public Health Service, who, as we shall learn, initiated the Framingham Heart Study. The trend, however, was long attributed by the medical establishment to artefact—to improved diagnosis in an aging population.

In 1950 Haqvin Malmros of Sweden published an influential report about spectacular wartime changes in CVD deaths in Scandinavia (Malmros 1950). He had made the important assumption that diagnostic custom and medical care changed little in his neutral country during the Second World War; therefore, the dramatic downward trend in reported CVD mortality in the war years was probably real. If real, it was probably due to wartime privations, among which Malmros (an internist trained in nutrition and biochemistry) postulated the role of decreased dietary fat consumption.

Others in Europe found a similar wartime picture, including reduced arterial pathology at autopsy. Their independent reports, indicating an abrupt sociocultural–environmental impact on CVD death rates and on the fundamental arterial disease itself, heightened awareness of the coronary epidemic and pointed both to its mutability and its possible causes.

An informal romantic period

As early as 1916, Cornelis De Langen, a young Dutch physician sent to teach medicine in Indonesia, was struck by the contrast among colonial Dutch and the native Javanese in the frequency

of angina pectoris, gall bladder disease, and post-operative thrombotic events, all of which he came to regard in the light of different lifestyles, diet, and blood cholesterol levels. He systematically made the seminal clinical and laboratory observations and then, to confirm them, went to a population of Javanese ship stewards living in a Dutch environment. From this, he proceeded to dietary experiments in which reversal of Dutch and Javanese habitual eating patterns produced profound changes in serum cholesterol levels (De Langen 1916).

De Langen's work is historically significant in the development of CVD epidemiology not only for its priority, scope, and use of several methodologies, but because its legacy can be traced in a direct line to the Dutch colleagues with whom he corresponded regularly: Isidore Snapper and Juda Groen. They, in turn, studied other contrasting populations and communicated their findings widely, influentially, and in English.

For example, De Langen's colleague and successor as house officer in Groningen was Isidore Snapper, who in the late 1930s became Rockefeller Professor in the Peking Union Medical School. There, Snapper undertook systematic study of ECG manifestations of coronary disease in populations and reported on their rarity in northern China. In 1941, in a book well-known to historians, *Chinese lessons to Western medicine*, he suggested that 'poor' working Chinese were protected from vascular disease by their mainly vegetarian diet, citing De Langen for priority in this view (Snapper 1941).

Juda Groen, student and colleague of both De Langen and Snapper, documented other dietary 'natural experiments'. He found, for example, lower blood cholesterol levels in vegetarian Trappists than in Benedictine monks and, at the Hadassah University Hospital in Israel, found lower vascular disease rates in Yemenite than in European immigrants to Israel (Groen *et al.* 1962; Kallner and Groen 1966).

The teachings and writings of this 'Dutch dynasty' touched the imagination of several pioneers of formal CVD epidemiology, particularly that of Ancel Keys, who had read both Snapper and De Langen when he met Groen in Amsterdam in 1952 and worked with him on a WHO expert committee in 1955 (personal communication 1955).

An early synthesis

Thus, Ancel Keys of Minnesota was well aware of this wartime mortality experience and of the early Dutch accounts. At mid-century, he and Paul Dudley White of Boston, based on their international eminence in nutrition and clinical cardiology, respectively, were invited around the world to witness contrasts in the prevalence of coronary cases and in diet and culture. Their early formulations about the influence of lifestyle on these differences led them to undertake and encourage others to take up formal epidemiological investigations. White and Keys promulgated an international strategy for CVD prevention, helped found and lead the new professions of CVD epidemiology and preventive cardiology, and effectively escorted these fields into the mainstream of international cardiology (Keys and White 1956).

The early era: 1948–72

Formal epidemiological research in cardiovascular diseases took several forms, beginning in 1948. Prospective study among defined cohorts, a 'new' strategy, focused on traits for individual risk within affluent, high-prevalence populations of the industrial world. Clearly, this summary chapter cannot give proper attribution to the many international investigations initiated early or late. Unquestionably, however, the prototype and icon of these was the Framingham Heart Study, discussed below (Dawber *et al.* 1951). Early studies, with similar design and intent to Framingham, spread rapidly across the USA and worldwide, as identified in Table 7.1.

Table 7.1 Early prospective (cohort) studies: 1948–72[a]

Alameda County Study	Honolulu Heart Study
Albany Civil Servants Study	Ikawa-Akita Study
Belgian Bank Study	Israel Ischemic Heart Disease Study
Bogalusa Heart Study	Lipid Research Centers Population Study
British Physicians Study	London Transport and Postal Workers Studies
Busselton Heart Study	Los Angeles Civil Servants Study
California Longshoreman Study	Malmö Study of Men Born in 1914
Charleston Heart Study	Minnesota Business and Professional Men Study
Chicago Heart Association Detection Project in Industry	NIHONSAN Study
Chicago Peoples Gas Company Study	Noichi-Kochi Study
Chicago Western Electric Study	Olmsted County Study
Community Syndrome of Hypertension, Atherosclerosis Study	Paisely-Renfrew Study
Cooperative Lipoprotein Study	Paris Prospective Study
Dupont Company Study	Puerto Rico Cardiovascular Disease Study
Evans County Heart Study	Seal Beach Study
Finnish Social Insurance Institution Study	Seven Countries Study
FINRISK Study	Stockholm Study
Framingham Heart Study	Tecumseh Community Health Study
Glostrup Study	United Airlines Study
Göteborg Study of Men Born in 1913	US Railway Study
Göteborg Primary Prevention Cohort Study	Western Collaborative Group Study
Harvard Alumni Study	Whitehall I Study
Helsinki Policemen Study	Yao-Osaka Study
Hisayama Study	Yugoslavia Cardiovascular Disease Study

[a]Initiated by 1972.

A different model, cross-cultural comparisons, was presaged by Epstein's study among New York City Italian and Jewish garment workers (Epstein and Boas 1955). But the icon of such formal studies is the Seven Countries Study, which began in the mid-1950s and is ongoing today. It also looked at individual risk prospectively within cohorts but focused main questions on the relationships between population-wide characteristics and CVD rates among cultures, in this case populations contrasting in habitual diet. It combined the goals of cohort studies with the older strategy of 'geographic pathology' (Keys *et al.*1970, 1980; McGill 1968).

Surveillance of CVD mortality was carried out in the early era, as it had been during the origins of CVD epidemiology, but trends in vital statistics on deaths continued to be treated as suspect by the medical community and were rarely examined systematically.

Experiment, also an early epidemiological thrust, was explained by Frederick Epstein in his Ancel Keys Lecture: '. . .a point is reached in the course of observational studies when it becomes
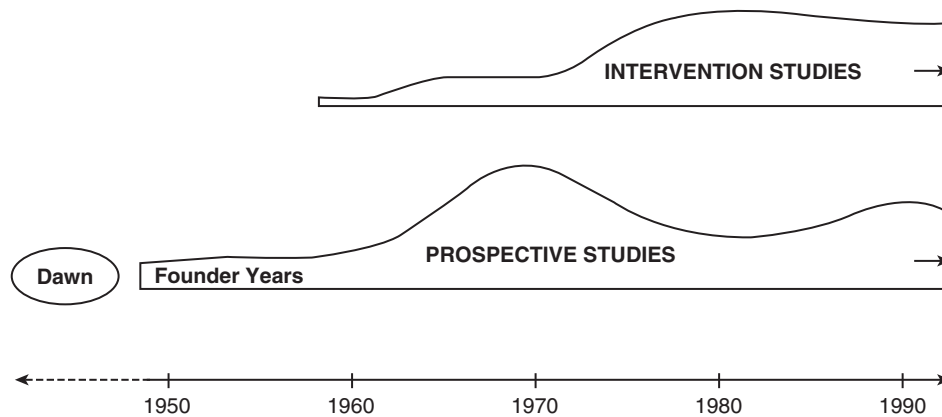
Fig. 7.1 Cardiovascular disease epidemiology historical development. Reproduced with permission from Epstein FH (1996). Cardiovascular disease epidemiology. A journey from the past into the future. Based on the 1993 Ancel Keys Lecture. Circulation, 93, 1755–64.

imperative to test whether predisposing factors not only predict clinical disease but whether their reduction causes a decline in the risk of disease' (Epstein 1996). In Fig. 7.1 from that presentation he depicted the time sequence of overlapping research strategies in CVD epidemiology, which coincides closely with the chronology conceived here.

Early trials of the effect of lowering of risk factors among randomized individuals or populations are listed in Table 7.2. Later and more definitive preventive trials are dealt with in appropriate detail elsewhere (Labarthe 1998; Black 2001; Steinberg 2005).

The core questions and the radiating arms of formal CVD epidemiology took form in the design, conduct, and analysis of these early studies that addressed the main candidate risk factors: blood pressure, diet, blood cholesterol, body mass, physical activity, and cigarette smoking. Such a broad new initiative required methods that were largely unfamiliar to the pioneer researchers. Soon, however, they learned and adopted elements of a common method and sound protocol (see Methods below).

The first formal cohort studies

A summary chapter cannot deal exhaustively with the myriad prospective studies that exploded from 1948 onward. Only a couple of these are discussed here because of their obvious priority in time or their role as prototypical of the genre.

The Minnesota Business and Professional Men's Study

The Minnesota Business and Professional Men's Study by physiologists Ancel Keys, Henry Taylor, and colleagues at the University of Minnesota examined 500 men in great physiological detail, annually from autumn 1947 to 1963, and followed them to 1983 (Keys *et al*. 1963). Though its epidemiological concept and prospective design provided a historical precedent for formal CVD studies, its resources and sample size were inadequate to produce predictive information until long after 'risk factors' were well laid out in larger cohort studies. The early Minnesota study, nevertheless, posed the appropriate questions about lifestyle risk factors; it defined 'norms', refined survey methods, and provided a stimulus and preparation for the Seven Countries Study and others that followed internationally.

Table 7.2 Early clinical trials in CVD risk factor reduction 1948–72[a]

Anti-Coronary Club Trial	Oslo (Leren) Diet-Heart Study
Bierenbaum St. Vincent's Hospital Study	Oslo Trial on Treatment of Mild Hypertension
Chicago Coronary Prevention Evaluation Program	Oslo Study of Diet and Anti-smoking Advice
	Physical Activity and CHD Pilot Trial
Coronary Drug Project	Program on Surgical Control of Hyperlipidemias (POSCH)
Finnish Mental Hospital Study	
Göteborg Multifactorial Primary Prevention Trial	Scottish Society of Physicians Clofibrate Trial
Hypertension Detection and Follow-up Program (HDFP)	MRC Low Fat Diet Trial
	MRC Soya Bean Oil Trial
Lipid Research (LRC) Coronary Primary Prevention Trial	Stanford Three-community Project
	Stockholm Prevention Trial with Clofibrate and Niacin
Lyon Mediterranean Diet Trial	
Morrison Diet-Heart Study	University Group Diabetes Program (UGDP)
Multiple Risk Factor Intervention Trial (MRFIT)	VA Cooperative Trials of Hypertension
Multifactorial CVD Prevention Trial in Helsinki Businessmen	VA Domiciliary Diet Trial
	WHO Cooperative (Clofibrate) Trial
National Diet-Heart Pilot Trial	WHO Collaborative MRF Trial
North Karelia Project	

[a]Initiated by 1972.

Of greater historical interest is how the Minnesota study was conceived in the first place. In 1948, Keys, who was a physiologist and nutritional scientist, had just completed a classic study of experimental starvation. In it, he had been struck by the rapid modifiability of heretofore-considered 'constitutional' characteristics such as body type, blood pressure, blood cholesterol, and vascular responses. Meanwhile, he had become curious about the phenomenon of epidemic heart attack, apparently from Minnesota newspaper reports of the day (Keys 1999). We know from an action photograph taken in 1946 that Keys had plotted a hypothetical projection toward intersection of the rising slope of heart deaths and the falling slope of other deaths in the city of Minneapolis. This antedated by two decades published discussions of 'the epidemiological transition' (Ancel Keys Photographic Archive, University of Minnesota).

Keys recounts in his memoirs:

> As news of the war and its aftermath receded from the newspapers, I was struck by the frequency of reports of executive men dropping dead, victims of what seemed to be a new plague, an increase in the frequency of coronary heart disease . . . . The cause … was unknown. I thought that we could record the characteristics of a large number of executives when they were apparently healthy, and then follow their status over the years, during which time some of them would develop coronary heart disease. By comparing the records of the afflicted men with those of the group that stayed healthy, we could discover which characteristics were related to the tendency to develop the [arterial] deposits.
>
> Keys (1999)

The Framingham Study

The Framingham Study was initiated by Joseph Mountin, Assistant Surgeon General, head of the Division of Chronic Diseases of the US Public Health Service (USPHS), and, according to his

contemporaries, an 'architect of modern public health' (Mountin 1956; Oppenheimer 2005). The special public health orientation and competence of Mountin and the original designers of that study set it apart from many others that sprang up around the world in the early 1950s.

Invited to Massachusetts by Harvard's David Rutstein, the proposed USPHS–community study set up shop in 1948 in Framingham, MA, a small, independent township near Boston, and, soon after, its management was incorporated into the National Heart Institute (NHI). There the study was redesigned by the NHI chief of biometrics, Felix Moore, and the first medical director, Gilson Meadors, who made estimates of the sample size required for a definitive study having the likelihood of establishing, in a 5- to 10-year period, the relationship of given characteristics to the risk of heart attack.

The original goals of the study were submitted to Bert R. Boone, Heart Disease Section, USPHS, in a letter of 19 July 1947, attributable to Meadors: 'This project is designed to study the expression of coronary artery disease in a "normal" or unselected population and to determine the factors predisposing to the development of the disease through clinical and laboratory examination and long-term follow-up of such a group'. In fact, the Framingham manual of operation listed 28 hypotheses specific to these possible characteristics of risk.

The same memorandum opined that there is no 'perfect sample' of a population and it went on to provide a further insight: 'It is of less importance to have such a [perfect] sample than to record rather accurately the characterization of the group studied'. Other pioneers who recruited the first CVD cohorts shared the view that bias of selection is diminished and generalization strengthened by large numbers, careful measurement, and long-term observation.

Early in-house opposition to epidemiological studies at the National Institutes of Health (NIH), by clinical and bench scientists, was overcome, in considerable part, by arguments of the Heart Institute's chief advisor and Advisory Council executive, the Boston cardiologist Paul Dudley White. Then, in 1950, a vigorous young internist in the USPHS hospital division, Roy Dawber, was appointed Framingham director and brought his practical ideas and management skills to the study. He set the tone of clinical relevance that Framingham has maintained over the decades (Dawber 1980).

Framingham and others of the original US cohort studies published an early monograph on the predictive power for heart and blood vessel diseases of blood pressure, blood cholesterol level, and cigarette smoking habit (Multiple authors 1957). A subsequent publication established Framingham investigators' priority in use of the term 'risk factor' (Kannel *et al.* 1961). These investigators went on to elaborate many of the central concepts and practical tools now employed in the identification of personal cardiovascular risk.

In the late 1960s, Framingham underwent a major crisis when powerful interests wedded to bench and clinical research at NIH, along with Nixon administration budget cuts, removed support for most of Framingham's staff. Roy Dawber and Bill Kannel, under official threats, valorously resurrected and then maintained the study in an arrangement between the National Heart, Lung, and Blood Institute (NHLBI) and Boston University that still thrives today.

The congruent findings from Framingham and other early analytical epidemiological studies worldwide (listed in Table 7.1) sparked a revolution in understanding of the risk of heart attack and stroke among 'healthy' populations. The findings of these pioneer studies, taken together, produced the 'risk factor paradigm', a concept of predictive factors along the causal pathways of CVD. This, in turn, provided an international framework for ongoing research questions on causation and for a generation of professional activity in CVD prevention. This risk idea and its quantitative evidence continue to provide the base for the academic discipline of CVD epidemiology, the specific indications for interventions on individual risk, and the stimulus for ongoing research and public policy in CVD prevention.

The Seven Countries Study

In the 1950s, a different epidemiological approach to understanding the causes of CVD focused on comparisons among whole populations across a wide spectrum of diet or lifestyle in efforts to define the mass, as well as the individual, characteristics related to high or low population risk. The Seven Countries Study tested specific hypotheses among largely rural, traditional populations contrasting greatly in habitual diet. It was carried out by Ancel Keys and international colleagues in a collaboration starting in the late 1950s and ongoing today (Keys *et al*. 1970, 1980; Kromhout *et al*. 2002). Major differences in CVD risk were found among samples of working middle-aged men followed for 30 years in 14 areas of seven countries, with the lowest rates in Japan and the Greek islands and the highest in the United States and Finland.

The Seven Countries Study provided the first credible data about major population differences in CHD and stroke rates. It also confirmed large variations in death rates from all causes. It found that a habitual diet of less than 10% calories from saturated fatty acids, with its associated lower blood cholesterol values, was apparently a necessary factor in lower population rates of CVD, whereas other risk factors failed to 'explain' the geographical differences. Within Seven Countries populations having different mortality, however, the 'traditional' CVD risk factors of diet, serum cholesterol, blood pressure, and cigarette smoking were universally predictive of an individual's risk, albeit with culturally different 'slopes' or force of the relationship (Keys *et al*. 1972; Kromhout *et al*. 2002).

The Seven Countries Study provided new and strong evidence for a policy of risk reduction at the population level. And it infected with the epidemiological method and mystique the medical and public health 'virgin forest' in each of its seven countries.

The spread of CVD epidemiology

Historical analysis remains to be made about how much of the rapid spread of CVD epidemiology in the 1950s was directly infective from the early foci in Framingham and Minnesota and how much was independent 'spontaneous generation'. Studies began early throughout North America and in the United Kingdom and Scandinavia and a little later in Japan. The London School of Hygiene and Tropical Medicine (LSHTM) was the nidus of early UK efforts as well as of much international enterprise in CVD epidemiology, based in the philosophy, research, and active teaching programme of Bradford Hill. He and his colleagues (see below) comprised a powerful academic centre of chronic diseases epidemiology, research, and training.

Of the many prospective, analytical studies initiated internationally in the early decades of CVD epidemiology (see Table 7.1), several became centres of ongoing academic activity and public health import. As relevant historically is whether the spread of CVD epidemiology was superfluous to the original investigations, whether 'merely' confirmatory or importantly contributory to the validation, strength, and generalizability of epidemiological method and the risk factor concept, or was the main value of its spread simply the alerting of professionals to their population's particular risk, with the knowledge they would need for regional preventive strategies? These issues beg historical analysis.

The evolution of risk factors

Ideas and evidence central to the evolution of the risk factor concept came mainly from (originally) non-epidemiologist investigators having particular interests or training in subject areas of CVD. Those include diet and nutrition, blood lipids and lipoproteins, blood pressure and 'hypertensive disease', obesity, metabolism, and diabetes, physical inactivity and fitness, respiratory disease and tobacco use, and various facets of the social, ethnic, psychological, and behavioural

picture intuited to affect CVD risk. Rapid advances in understanding in this early period came from the ability of some of these investigators to move comfortably between the clinic, the laboratory, and populations in the field, or to collaborate effectively across disciplines (Gofman *et al.* 1950; Keys and White 1956; Morris 1957).

Therein lies much of the rich content as well as the *Sturm und Drang* of CVD epidemiology, which, again unfortunately, defies reduction for this summary chapter. For insights into the active to and fro among disciplines in the investigation of specific risk characteristics in CVD pathogenesis and prevention, I recommend a few recent reviews: physical activity, Lee *et al*. (2006); lipids, Steinberg (2005); all risk factors, Labarthe (1998) and Stamler (2005).

Method, design, analysis, and computation

The naïvety of pioneer investigators about epidemiological methods led to increased communication among them, then to improved methodology. A certain collegiality emanated from early conferences on survey methods, study design, and work-in-progress. These were held by the WHO in Geneva from 1955 onward, at Beaconsfield in 1957, Princeton in 1959, at annual AHA meetings starting in Chicago in 1960, early on and at regular intervals at the LSHTM, and in expert groups of the International Society of Cardiology (ISC).

Essential to the comparisons of early CVD prevalence surveys and the prospective studies that followed were pioneer contributions made to standard, validated survey methods, including symptom questionnaires, blood pressure and other physical measurements, the electrocardiogram, blood lipid and other chemical measures, and diagnostic criteria. Diagnoses made in prior surveys and recorded in death certificates were poorly repeatable and of uncertain validity. By contrast new field methods were rigorously and systematically developed, often collaboratively among the WHO, the LSHTM and St Thomas's and Guy's Hospital in London, the Laboratory of Physiological Hygiene in Minnesota, and committees of the AHA and the ISC (Holland 1962; Rose and Blackburn 1968).

In the early 1960s, those caught up in the new field of CVD epidemiology were suddenly able to put aside their cumbersome mechanical calculators and start sorting punched cards to get their row and column sums, summed squares, and products. But no sooner had researchers become comfortable with cross-classifications and chi-square statistical tests of differences, two variables at a time, than electronic computers burst upon the scene, rapidly expanding the horizons of computation and inference. Computer facilitation of data storage and management, of computation of correlations and regressions, along with the capacity for handling multiple variables simultaneously, was technically akin to its contemporary phenomenon of blasting off into space!

Electronic computers made possible one of the major contributions of modern epidemiology, that is, analysis of the effect of multiple variables while adjusting for their interactions. For example, the multiple logistic regression was first implemented in CVD epidemiology by Jerry Cornfield (Truett *et al.* 1967), soon followed by Cox's proportional hazards ratios and life table regression (Cox 1972).

Bradford Hill is given the credit for assimilating epidemiological–statistical methods from the past and developing new methods for improving the design of observational studies, for the design and analysis of randomized clinical trials, and for compiling the now-classic considerations for causal inference from statistical correlations in observational studies. His pioneering study of a cohort of British physicians and their smoking habits made a dramatic impact on design in epidemiology as well as on knowledge about the use of tobacco in relation to CVD and lung cancer (Doll and Hill 1954). Hill also trained many pioneers in chronic diseases epidemiology.

Jerry Morris's study of London Transport workers similarly provided innovations in the design and early understanding of the limitations of occupational studies for causal research in CVD epidemiology as well as early evidence about the role of habitual physical activity as a risk factor (Morris *et al.* 1953).

Automated chemistry vastly improved the reliability and efficiency of survey measurements as did the role of the WHO, the NIH, and Centers for Disease Control (CDC) in providing laboratory standards, testing, and manuals for survey methods.

The central role of the evolution of design and analysis in the development of modern epidemiology is, however, beyond the scope of this summary (see Conceptual evolution below).

Institutions and support agencies

Governmental support agencies, WHO, and heart foundations internationally were crucial to the rapid and effective progress in CVD epidemiology and prevention research. Each organization had particular ways of operating, funding assets, strengths, and institutional 'personalities'. Mainly they were complementary in roles of advice, design, funding, coordination, and direction.

The WHO

The efforts of the WHO in CVD prevention research and programmes were fostered from the outset by an international community of its supporters and consultants. The WHO responded by assembling experts in prevention research and policy and by establishing, in 1957, a CVD section at its Geneva headquarters and an operational European office in Copenhagen.

The first WHO CVD director, Zdenek Fejfar, organized timely expert reports and manuals on epidemiological methods, study design, and procedure, defining major CVD problems and enlisting expert solutions. In 1964, he commissioned *Cardiovascular survey methods*, initially a collaboration of the LHSTM and the University of Minnesota, now in its third edition, which provides detailed formularies, criteria, and a bare-bones standard strategy for surveys (Rose and Blackburn 1968; Luepker *et al.* 2004).

The WHO also initiated and coordinated major pioneering collaborative studies: the first cholesterol-lowering trial (the Clofibrate Trial) in the 1960s, and the European Multiple Risk Factor Intervention Trial in Industry in the 1970s, each among the earliest experimental interventions on risk; the Myocardial Infarction Registers organized by the Copenhagen office in the 1970s, and more recently, the MONICA Project, among the few research-oriented approaches to CVD surveillance, which provided systematic analysis of international disease trends.

The UK Medical Research Council (MRC)

The MRC was formed in 1913 as the Medical Research Committee and incorporated as the Medical Research Council by Royal Charter in 1920. In the 1950s, in parallel with the British National Health Plan, the MRC undertook to stimulate and fund research in chronic diseases. Several early units had a strong epidemiological and social medicine focus, one a Statistical Research Unit at the LSHTM under Bradford Hill with Richard Doll, another a Social Medicine Research Unit under Jeremy Morris at the London Hospital Medical School, and finally an Epidemiological Research Unit under Archie Cochrane at Cardiff, with Ian Higgins and William Miall. All had more or less orientation toward cardio-respiratory problems and pioneered in CVD surveys, prospective studies, and trials among civil servants and in the population of the Rhondda Fach (Higgins *et al.* 1963).

MRC units developed in other parts of the UK and Commonwealth, including Scotland and Jamaica, studying local vagaries of CVD and conducting trials, including the treatment of mild hypertension.

US National Institutes of Health (NIH)

The NHI opened as a new institute of the NIH in 1948, with a mission to support extramural research in CVD. From the outset it established a balanced strategy of support for clinical, laboratory, and epidemiological research and soon took jurisdiction over the Framingham Heart Study. James Watt, an epidemiologist and early institute director, strengthened the policy and organizational base of the population approach to research at the Heart Institute, at WHO, and internationally (personal communication James Watt to Zdenek Fejfar, 1959).

The eventual NHLBI became an international engine of epidemiological and prevention-related research, in which it has led its sister institutes and the larger community. As pointed out below, while it led the field, it wrestled with the expansion of costly population studies and trials and became more directive of them under the guise of 'fiscal responsibility'.

Heart foundations

In the early twentieth century, public health-oriented cardiologists within the New York Heart Association influenced its restructure into the AHA. The leaders of the AHA, in turn, championed its conversion into a public agency in 1948. The broad community views and initiatives of these leaders, particularly Felix Moore and Oglesby Paul, eventually led, in 1964, to formation of a Scientific Council on Epidemiology and Prevention having active programmes in research communication, methodology, and training. It became the parent body and philosophical home of CVD epidemiology in North America.

Guided by Paul Dudley White and Ancel Keys, the ISC, a consortium of regional professional societies, began research programmes and formal training in CVD epidemiology in the 1950s and 1960s. These leaders co-opted the cardiology elite into conferences on design and methods; they organized international seminars on CVD prevention; and they moulded the ISC into scientific councils with research and training missions. The ISC, joined by national heart foundations to become the International Society and Federation of Cardiology, was further reformed as the World Heart Federation in the 1990s and continues to support international seminars in CVD epidemiology. Several of its component regional foundations, such as the European Society of Cardiology, have organized active working groups to forward research and training in CVD epidemiology and prevention.

Academia and CVD epidemiology

Formal training programmes in observational CVD epidemiology and clinical trial design and analysis were among early and influential academic developments in the epidemiology of non-communicable diseases. The LSHTM pioneered in this development in the mid-1960s, initiating short courses, led by Donald Reid and Geoffrey Rose, which attracted an international audience.

The ISC research committee organized the first international Ten-day Seminar in CVD Epidemiology in 1968, which was led by Geoffrey Rose, Richard Remington, Jerry and Rose Stamler, and later by Darwin Labarthe, Dag Thelle, and K. T. Khaw. It is on-going almost 40 years later. With its regional counterpart at Lake Tahoe in the USA and other language-specific regional seminars, this seminar has exposed hundreds of younger CVD investigators from many countries to rigorous exercises in literature criticism and study design. Seminarians gain a new view of population strategies and preventive practice and, as alumni, form an international core of academicians and practitioners who foment epidemiological research and forward prevention policy and practice.

Many schools of public health and medical faculties maintain active research programmes, and graduate and post-doctoral training and degree programmes with majors in CVD epidemiology, which serve as models of training in epidemiological research for other chronic diseases.

Numerous texts and reviews in CVD epidemiology and in preventive cardiology have wide readership.

The modern era: 1972–present

Formal prevention policy and trials of the 1970s

The early 1970s marked a dramatic period of transition in CVD epidemiology; that is, between the period producing the evidence that formed the risk factor concept and the launching of the prevention policy and broad action implicit in the risk paradigm.

In particular, there was an uncomfortable interim in the USA while the National Diet–Heart Pilot Trial underwent a succession of evaluations after its results were published in 1968, accompanied by strong recommendations for a definitive diet–heart trial (National Diet–Heart Study Research Group 1968). It was finally and irrevocably deemed infeasible as a blinded, single-factor, diet–heart trial by an NIH task force led by E. H. Ahrens, Jr. This was based purportedly on practical issues of staffing and cost rather than on the scientific validity of its design or the public health import of diet in CVD. (Another appropriate and fascinating subject for historians would be the decisions, manipulations, and consequences surrounding that NIH decision.)

Frustration among the prevention research community during that period came from the inability to elicit any clear governmental policy on CVD prevention, either in research or programme, when the Lalonde Report had come out in Canada and when the AHA, the WHO, and other non-governmental agencies had called vigorously for a broad public policy and programme in CVD prevention. The medical establishments and governments of the USA and Europe seemed to drag their feet, unprepared either to accept the congruent evidence supporting prevention and to back lifestyle changes for the public or, its logical alternative, to authorize further preventive trials of risk factor modification.

In response, a band of pioneers in prevention mobilized efforts to stimulate the needed grand plan for research and policy, resulting in the following actions internationally:

◆ The Report on Preventive Trials in Coronary Heart Disease, from the ISC Conference in Makarska in 1968, recommended specific single and multiple risk factor trials of primary and secondary CVD prevention. The meeting and report were directly influential in subsequent policy decisions at the NIH, WHO, and internationally.

◆ Pioneer epidemiological researchers, Richard Remington, Jeremiah Stamler, and Henry Taylor, with a band of expert collaborators, submitted a proposal to NIH in 1969, dubbed 'Jumbo' because of its immense size, for a primary prevention trial to lower multiple risk factor levels, as the more powerful and efficient approach to 'prove' the feasibility of CVD prevention. ('Jumbo' was rejected, but helped stimulate a policy response. Requests for proposals for such a trial, and others, were finally issued from NIH in 1972.)

◆ The WHO sponsored several initiatives in 1970–71 on individual and industry-based multiple risk factor trials of both primary and secondary prevention.

◆ The US Joint Commission on Heart Disease Resources published its seminal report of recommendations for major research and broad social strategies of CVD prevention (Inter-Society Commission for Heart Disease Resources 1970). (No prevention policy recommendations before or since have been nearly as comprehensive.)

◆ The 1971 report of the National Heart and Lung Institute (NHLI) Task Force on Arteriosclerosis, in conjunction with the Joint Commission Report and clamour from the scientific community, led Theodore Cooper, the NHLI director, to propose major national policy for CVD prevention in 1972 (National Heart and Lung Institute 1971).

'A giant leap for mankind'?

These activities all converged in a new and international wave of research policy and action that at the time was considered a great step forward for CVD epidemiology and prevention. Some, however, found that the new direction toward experimental 'proof' was redundant to the clear findings of observational epidemiology, which, in turn, were congruent with clinical and laboratory evidence about the causes of CVD. Many of the subsequent generation of preventive trials proved to be academic and costly and a diversion from the socially oriented research and health promotion programmes that many CVD epidemiologists thought justified by the evidence. But the die was cast.

Gigantic trials, both explanatory and pragmatic, were undertaken in many places in the next decades (too extensive to document here) to modify single and combined risk characteristics in simultaneous efforts to prove causation and test the feasibility and safety of secondary and primary prevention of CVD (Blackburn *et al.* in preparation). They occupied the resources and energies of much of the cardiovascular research community worldwide. These ponderous, multi-centre, 'government issue' approaches were in many respects inimical to investigator initiative, coherence, and efficacy; their eventual outcomes were sometimes ambiguous. But they were essential, in the tenor of the times, to enlist the medical establishment in prevention. They became 'the only show in town' for academic CVD epidemiology; almost everyone 'got on board'.

The Lipid Research Centers (LRC) Primary Prevention Trial, part of a vast NHLBI–LRC empire internationally, at long last 'proved' the effectiveness of lipid lowering as a prevention strategy to reduce coronary risk (Lipid Research Clinics Program 1984). The Hypertension Detection and Follow-up Program, carried out in the same period, 'proved' the beneficent effects of a 'community approach' to hypertension control, while parallel British and Australian hypertension trials found drugs better than placebos (Black 2001).

On the other hand, these 'successful' 1970s trials substantially determined the overwhelmingly medical–pharmaceutical orientation, or 'medicalization', of subsequent CVD prevention policy and programmes in much of the industrial world.

A population strategy of CVD prevention emerges

As the risk factor paradigm from CVD epidemiology became more generally accepted, leaders and institutions moved forward with new prevention strategies. Policy-makers sought to integrate the traditional medical approach—to lower risk in the high-risk individual—with a complementary and more powerful population-wide health promotion strategy. This idea grew through several iterations until elaborated most clearly by Geoffrey Rose and colleagues in a WHO Expert Report on the population strategy of CHD prevention (World Health Organization Expert Committee on the Prevention of Coronary Heart Disease 1982) and in Rose's post-retirement classic, *The strategy of preventive medicine* (Rose 1992).

Another fundamental preventive strategy was formulated in 1978 by Toma Strasser at WHO, who proposed the term 'primordial prevention' to denote prevention of the epidemic occurrence of elevated CVD risk factors themselves—an alternative to detection and treatment once they are present. This was seen as a possible means for 'preserving entire risk-factor-free societies', thereby averting expansion of CVD as a global health problem (Strasser 1978).

Frederick Epstein, in particular, extended this idea, based on evidence that stopping smoking, modifying eating patterns, controlling hypertension, and improving physical activity and weight control, would profoundly reduce the age-specific rates of many common causes of mortality, including some cancers (Epstein 1994). This broader concept was stimulated further by evidence from several sources: the low-CVD-risk societies found in the Seven Countries Study, which

often had lower all-causes mortality as well (Menotti *et al.* 1987), and Stamler's findings on the small but impressive very-low-risk segment of American cohorts (Stamler *et al.* 1993). Epstein proposed that this concept be explored with health promotion in whole populations as well as in youth, gender, and ethnic subgroups threatened but not yet at high CVD risk (Epstein 1996). (Epidemiological interest in recent years has extended toward prediction of all-causes deaths and longevity, to analysis of trends in risk and disease rates and their possible explanation, and to the impact of prevention on the population age pyramid. It is appropriate, therefore, to continue to ask what, indeed, are the ultimate aims of 'prevention'?)

Global health policy for CVD prevention gained support from Omran's 'theory of epidemiologic transition' (Omran 1971), which forecast mounting proportions of deaths from CVD in all regions of the world due to rising burdens of 'man-made and degenerative diseases'. Policy development continues to the present day, building on accumulated knowledge and experience, expressed in landmark reports such as 'International action on cardiovascular disease: a platform for success based on international cardiovascular disease (CVD) declarations' (International Heart Health Society 2005), and in a number of specific national plans.

'The decline' (in CVD mortality rates)

It was in this period of the 1970s that the decline in age-specific mortality rates for coronary heart disease, having first been observed in the 1960s in California, was belatedly recognized throughout Western industrial society. This remarkable course correction in a raging non-communicable disease epidemic has become a major impetus to international research and policy for CVD prevention, leading to international conferences on 'the decline' and to the evolution of systematic surveillance research and strategies of disease monitoring (Gillum *et al.* 1984; The ARIC Investigators 1989; Tunstall-Pedoe 2003).

These programmes have documented the decline in CVD mortality rates in many countries and the equally dramatic rise in others such as the Eastern Block in Europe and in the developing world. They have established clearly that population strategies of risk detection and health promotion, and innovations in medical and surgical cardiac care, have each contributed substantially to the decline in CVD mortality rates. Again, the limits of space prevent elaboration of the specific improvements in public health and in cardiac care that are documented to have reduced mortality and improved survival rates from CVD.

The challenge to epidemiology has been to explain the trends, that is, to link preventive programmes or trends in mass health behaviours such as eating and smoking patterns, and levels of specific risk factors, to the trends in incidence and mortality rates. Research on CVD surveillance, with modelling of risk change effects, has entered the evolution of methods for modern epidemiology. These, in turn, are significantly led by work in CVD epidemiology.

'Circular epidemiology' and community studies of the 1980s

The first generation of preventive trials was followed by a period of elaboration of the risk factor paradigm that some called 'circular epidemiology', going 'round and round' on the same old issues (Kuller 1999). In an effort to move beyond repetitive cohort studies and trials, at least two other major directions were taken in the 1980s: in a few centres in the USA, Europe, and South Africa, large-scale, 'quasi-experimental' public health trials or community demonstrations of CVD health promotion strategies were approved after extensive peer review (Winkleby *et al.* 1997). In parallel, formal surveillance programmes were established to document and attempt to explain the dramatic international trends in CVD death rates that had begun in the 1960s (Gillum *et al.* 1984; Tunstall-Pedoe 2003).

Many of these preventive and epidemiological undertakings, too, were large and expensive, and again, some had ambiguous results. For example, the designs and interventions of the public health trials in California, Minnesota, and Rhode Island were insufficiently powerful to demonstrate significant short-term treatment effects over and above the dynamic trends on-going in health behaviour that were lowering risk levels throughout the industrial West in the 1980s (Winkleby *et al.* 1997). Few in the medical establishment accepted the community trial findings in Finland and the USA for what they really were: strong documented evidence for a profound change in health behaviour and CVD risk at ground level, irrespective of any true experimental effect.

An unintended consequence of the two decades of large and expensive CVD population studies and trials was mobilization of a powerful bench and clinical elite against what they termed 'those huge, costly, everlasting, epidemiological projects', along with calls for their rapid 'sunset' (personal communications to the NHLBI Advisory Council, multiple authors, 1988–92). It may be that the prevention research community has not fully recovered from the fallout of this sometimes rancorous rally against funding for CVD epidemiology in the late 1980s and early 1990s.

A millennial pause in the 1990s

At the moment in history when age-specific CVD mortality rates were in maximal decline in much of the West, and when the potential for prevention was clearly an open, if not guaranteed, opportunity, a reversal of fortunes in CVD epidemiological and prevention research developed, both in policy and programme. An opinion vigorously registered by the head of the 1991 NHLBI Task Force on Research in Atherosclerosis characterized attitudes of the clinical and bench scientific establishment at that juncture. He remarked to the effect that: 'Epidemiology made its contribution in the '60s and '70s. Now there are more interesting and important things to do' (personal communication, Daniel Steinberg, *circa* 1992).

That 1991 Task Force report was the first in the series of these influential milestones in US national research policy that failed to describe continued needs for epidemiological study or to maintain the balance among research disciplines in NHLBI programmes and policies, a policy highly productive over the prior decades. This departure represented a deliberate and qualitative change in national research policy for atherosclerotic–hypertensive cardiovascular diseases.

My Ancel Keys Lecture of 1991 summarized the unrest pervading the CVD epidemiology community in response to that official rejection of research balance as well as to NIH budget straits and the 'sunset' mentality of shutting down existing research. It also addressed increasing and discriminatory NHLBI restrictions on, and control of, epidemiological studies and trials. And it cited a general regression in energy, funding, and status of population research implicit in the national focus on individual, medical, and high-tech approaches to cardiological care and prevention (Blackburn 1992).

Subsequent calls for action by the epidemiological community caused the director of the NHLBI to assemble in 1992 an *ad hoc* 'Task Force on Research in Epidemiology and Prevention of Cardiovascular Diseases', a ploy that calmed the waters but avoided the basic issues of institute policy inimical to epidemiological research (National Heart, Lung, and Blood Institute 1994). Millennial unrest in the US academic community of CVD epidemiology was further diverted when Clinton and then Bush administration proposals were carried out to 'double the NIH budget in 5 years'. More people, in the USA, for a little while, got a larger 'piece of the pie'.

Internationally, where most countries never 'had it good' in the first place from strong government policy or funding on prevention, the picture of CVD epidemiology and prevention research has remained more or less static.

Progress, nevertheless

I should not exaggerate. Many positive elements are noted from the 1990s and since the millennium. CVD mortality rates have continued to decline in many countries, though at a slower rate. (Exceptionally, they have climbed steeply in eastern Europe, India, and southern Africa.) Epidemiological evidence has accumulated that CVD risk factor modification substantially reduces the risk of many non-CVD illnesses including some cancers; that is, it reduces total mortality. And the interchange among epidemiology, clinical, and bench science has become more natural and productive.

Epidemiology also made substantial specific contributions to a revived interest in the role of inflammation in atherosclerosis and thrombosis. Epidemiology and trials extended knowledge of the effects of diet independent of lipids and they led to effective use of prevention strategies in those at highest risk, such as patients with diabetes and renal disease. New interpretations of observational evidence increased the appropriate use of absolute over relative risk in efficacious prevention strategies. And epidemiology produced evidence about social inequities in risk, coming up with serious projections for CVD epidemics in the developing world.

Meanwhile, in the 1990s, the mature academic field of CVD epidemiology was having internal perturbations, including self-criticism of its 'circular' pursuits: study of 'the same old', or slightly refined, add-on risk factor analyses. Searching for the 'new', researchers faced the magnetic attraction, both intellectual and economic, of priorities in the gene–environment questions of individual CVD risk, finding direction in these mechanisms rather than in those of societal risk. Such a direction appeared to flourish within a social milieu preoccupied with medical–pharmacological approaches to individual and even population-wide risk, amidst a wider culture in which 'personal responsibility' for health trumped social obligation.

Post-millennial trends for the 2000s

CVD epidemiology remains a vigorous discipline of non-communicable disease epidemiology. The high quality and number of abstracts and publications submitted to the major scientific assemblies and journals concerned with CVD is evidence of progress. The youthful composition of those assemblies and of the regional and international Ten-day Seminars in CVD Epidemiology also is a positive sign. Observational epidemiology maintains fairly stable governmental review and absolute funding levels, despite rigid new policy rules and 'programme priorities'. A few centres remain productive with cohort studies addressing poorly understood issues of socio-economic class and CVD risk. Clinical trials, with a few happy exceptions such as the DASH study of diet and blood pressure, no longer mainly test hygienic or public health interventions but rather are drug-related and increasingly supported by industry.

Innovative epidemiological strategies abound, such as postal surveys and trials, with long-term follow-up among massive numbers of responsive professional men and women; nested case–control studies within older survey and cohort populations; international multicentre and cross-cultural surveys and clinical trials; meta-analyses of worldwide cohort and trial data; systematic international and regional surveillance studies; and an occasional group-randomized trial of health promotion.

Faculty positions and graduate and post-doctoral training programmes in CVD epidemiology remain stable, their collaborations increasing with genetics, physiology, metabolism, clinical trials, and 'clinical research'. Many branches of medicine, even surgery, now proudly proclaim the goal of prevention. Thus, the picture is far from bleak, though research funding for CVD epidemiology and prevention is far from plentiful. It remains perennially incommensurate with the disease burden.

The conceptual evolution in CVD epidemiology

Concepts have evolved steadily in CVD epidemiology, along with new evidence, methods, and professional training. Problems of design and analysis central to the whole field of epidemiology are increasingly recognized and dealt with as analysts (and their computers) acquire greater sophistication. 'Over lightly' the following conceptual issues evolve:

◆ Bias and confounding continue to be the main livelihood of epidemiological theorists and methodologists.

◆ Regression–dilution bias, the great weakener of epidemiological evidence, is systematically corrected.

◆ The funnel-shaped relation between precision, significance, and sample size is explored.

◆ Meta-analysis has left the realm of the investigator and moved to world centres that aggressively acquire and reanalyse everyone else's data.

◆ The old intellectual hierarchy of case–control versus cohort study versus randomized trial is challenged when their risk estimates are found increasingly similar as study design and methods improve.

◆ The provenance and training of epidemiologists shifts such that knowledge of the biology and mechanisms of disease phenomena can no longer be assumed. (And its absence is found disadvantageous to good study design and interpretation.)

◆ Clinical–laboratory–epidemiological cross-fertilization and collaboration increases.

◆ Separate and complementary roles of individual and ecological correlations are appreciated.

◆ Low CVD risk is found among entire populations and in low-risk segments of high-incidence populations, confirming and strengthening the risk paradigm.

◆ Criteria are honed for enhanced causal inference from observational evidence.

◆ The generalizability is increasingly questioned of experimental 'proof' from the 'platinum meter' of clinical trials (always carried out in select populations).

◆ The ultimate role of epidemiology is appreciated: to establish real-world implications of small-world evidence, and so on!

Leitmotifs in CVD epidemiology

The medical establishment has traditionally been slow to accept epidemiological evidence on diet and culture among the basic causes of atherosclerosis and CVD. The more favourable interpretation of this incomprehension is the 'necessary' medical focus on care rather than prevention and on the individual rather than the collectivity. In any case, recommendations for diet and lifestyle change in the general population, even when based on congruent evidence, have been unsupported by traditional medicine without 'conclusive proof' from human experiment, proof that is often infeasible, costly, or unethical to attain.

Such attitudes are, at best, an ongoing symbolic challenge to epidemiology, but they are also a significant impediment to reasoned public policy based on the best available evidence at any given time.

Another leitmotif in the development of modern epidemiology is its struggle for recognition as an essential basic science as well as a utilitarian applied science. Epidemiology continues to fight for intellectual and administrative equity within institutions and their policies. Among the three medical research disciplines 'We are number 3. Thus, we try harder!'

Clearly, such issues at the heart of modern epidemiology justify more thoughtful treatment and historical analysis than this summary presentation allows.

Epilogue

CVD epidemiology in the new millennium has evolved into a productive and mature discipline paralleled by rich findings from clinical and laboratory researches and, *pari passu*, a decline of CVD mortality rates in many places.

Historically, the field is unique in its origins and in its contributions to the concepts, evidence, and methods of modern epidemiology. But while epidemiology has helped establish the promise of population-wide prevention and has led medical science and public health to the brink of its accomplishment, actual research and programmes for effective population control of the CVD epidemic have languished.

Molecular biology, which for a time has dominated CVD research, enhances the understanding of mechanisms of disease and ultimately is expected to improve medical practice. On the other hand, the relevance of studies in gene and gene–environment associations to the mass causes and prevention of epidemic CVD is under question. Left to future judgement is the wisdom of a deliberate shift of intellectual focus, energy, and national policies away from the challenge of population-wide primary prevention and toward high-tech medical strategies and the biogenetics of personal risk and 'resurrection'.

Today's challenges for CVD epidemiology include the effects of 'incomplete prevention'. In that current state, the decline in mortality rates slows (at least, in the USA), while improved survival along with stable incidence rates tends to expand the CVD burden among aging affluent populations. Further progress in prevention at the population level requires priority for research into risk inequities and prevention strategies among youth, the elderly, women, and minorities, and into the looming threat of epidemic CVD in developing countries. There, high rates of tobacco use and of hypertension wait ominously for the projected upward shift in the distributions of risk factors related to diet and physical activity.

The history of CVD epidemiology strongly suggests, nevertheless, a continuing opportunity, achievable through scientific research and its fruits, for another global epidemiological transition—to longer, healthier, and different lives.

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