A Quarter-Millenium of Cardiovascular Epidemiology

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Abstract: According to George Rosen the roots of Epidemiology lie in the mid 17th century, although Hippocrates was aware of some of its methods. Cardiovascular Epidemiology can be traced back to the mid 18th century to the pioneering contribution of William Heberden (who coined the term 'angina pectoris') and John Fothergill. Proudfit in 1983 cited Jenner, Parry, Burns and Black as the originators of the ischaemic theory of angina pectoris. Of these four, Samuel Black's observations displayed a particularly epidemiological bent and he was the first to notice 'the French Paradox'.

The description of myocardial infarction in living patients was not made until the late 19th century. It was Sir James Mackenzie's community studies of disease in Scotland which ushered in modern Cardiovascular Epidemiology. His work influenced Paul Dudley White who was instrumental in the Framingham Study, where the term 'Risk Factor' was first applied to cardiovascular disease, and involved at the inception of the Seven Counties study.

Over the second half of the 20th century the number and types of epidemiological studies mushroomed, but it is beyond the scope of this review to cover them exhaustively. We are now in the era of genomics and witnessing an 'Epidemiological Transition.'

GENERAL BACKGROUND

In their 'Foundations of Epidemiology,' the Lilienfelds have an important chapter entitled 'Threads of Epidemiologic History' which traces [1] epidemiology back to Daniel Bernoulli in the 18th Century and through La Place, Poisson and particularly Louis to the 'European Students' of the 19th century. These include William Guy, John Simon, William Farr and William Budd; and the 'American Students,' Elisha Bartlett, George Shattuck, Francis Delafield and Alonzo Clark. In fact, observations on mortality and demographics had been made earlier by two friends: William Petty and John Graunt [2]. Petty was the father of 'Political Arithmetic' a term which he invented, signifying data collection on population, education, revenue, disease and similar topics. As well as constructing the first 'life table,' Graunt formulated a law which states [3] that fashions in the nomenclature of disease can play havoc with mortality rates. Francis Bacon, who developed inductive logic, was to influence the development of epidemiological methods from the 17th century [1], as was the publication of John Stuart Mill's 'A System of Logic' in 1843 [4].

The London Epidemiological Society, founded in 1850, was the first of its kind anywhere and had as its main thrust the control of water-borne infectious diseases - notably cholera [5]. Its first President was Benjamin Guy Babington and John Snow was one of its many Vice-Presidents. The evolution of the term 'epidemiology' is interesting, as the first reference to it in the Oxford Dictionary was not until 1873 [6]. Perhaps the 'Epidemiological' in the Society's name is its first coinage as 'epidemical' was used up to this time; the French 'épidémiologie' appeared first in 1855 [7]. As we have seen, epidemiological techniques and their application to improving the public health flowered in the mid 19th century in response to infectious disease. There were, however, earlier initiatives in the unravelling of the epidemiology of cardiovascular disease.

EARLY CARDIOVASCULAR EPIDEMIOLOGISTS

William Heberden, Physician to the Lexicographer Samuel Johnson, described osteoarthritic nodes [8], and in 1768 coined the term 'angina pectoris' [9]. By providing a description of the disease, albeit incomplete, Heberden had performed the invaluable epidemiological service of providing a definition of the disease for future study. By the time of his death he had seen almost 100 cases of angina pectoris, only three of whom were women.[9] It has been claimed that Nicholas Rougnon described angina five months earlier than Heberden, but this has been disputed [9].

Proudfit mentions [10] that the English Physician, John Fothergill, first observed angina before 1756 and appears to have suggested its cardiac origin. Booth, in 1757 [11], felt that Fothergill was the first to establish the link between angina pectoris and diseased coronary arteries. Yet despite his previoss assertion Proudfit goes on to state that [10] the origin of the concept of the ischaemic theory of angina pectoris can be traced back to four doctors working in the British Isles: Edward Jenner, Caleb Hillier Parry, Allan Burns and Samuel Black. Proudfit maintains [10] that they developed the concept over a period of 23 years around the turn of the 19th century.

Edward Jenner, a protégé of the great surgeon John Hunter, made the connection [10] between ossified coronary arteries and angina pectoris in 1788. He had been dissecting a case, "When my knife struck against something so hard and gritty, as to notch it. I well remember looking up to the

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ceiling, which was old and crumbling and conceding that some plaister [sic] had fallen down. But on a further scrutiny the real cause appeared: the coronaries were become bony canals then I began a little to suspect." This was contained in a letter to his younger colleague and friend, Caleb Hillier Parry, but was never sent, as "At this time my valued friend MR JOHN HUNTER began to have the symptoms of angina pectoris too strongly marked upon him; and this circumstance prevented any publication of my ideas on the subject as it must have brought on an unpleasant conference between MR HUNTER and me." In 1793, Hunter dropped dead after an argument at a meeting in St George's Hospital, London [12].

In 1788, Parry, read a paper on angina pectoris at the Fleece Medical Society, a small medical club in the South west of England [10]. In his book on 'syncope anginosa' in 1799, he mentions that Dr Black communicated a case of angina pectoris to the London Medical Society six years afterwards which stressed the possible association of angina pectoris with ossified coronary arteries, but it is very clear that Dr Black was working in isolation and did not know of the other men's findings. John Hunter performed the dissections for Heberden and Fothergill [11] and was Jenner's mentor. In his book, Parry, omitting Fothergill gave his friend Jenner the credit for connecting angina with the heart [9]: "It was suggested by Dr. Jenner that the angina pectoris arose from some morbid change in the structure of the heart, which change was probably ossification, or some other disease."

Allan Burns was a Glaswegian pathologist who at the age of 28 years, in 1809, published a book on diseases of the heart, which contained a chapter, *'On Disease of the Coronary Arteries and Syncope Anginosa.'* Proudfit attached [10] great importance to Burns' contribution but, it should be noted that no less an authority than Thomas Lewis was dismissive of Burns as he felt he was merely recycling Parry's observations [13].

Samuel Black is mentioned in an article by John Warren, entitled 'Remarks on angina pectoris,' in the January 1812 issue of the New England Journal of Medicine and Surgery, which Warren founded (subsequently, as the Boston Medical and Surgical Journal it was purchased by the Massachusetts Medical Society for $1 in 1921 and changed its name to the New England Journal of Medicine in 1928 [14]). Warren's article was reprinted in the sesquicentenary edition [15], alerting the modern world to Samuel Black's work. Samuel Black was born in 1763/4 in Dromore, Co Down [16]. He attended Edinburgh University from 1782 until 1786, graduating with an MD. He entered Clinical Practice in Newry, Co Down in 1792 and published the first of his four cases of angina pectoris in 1795; he died in 1832. In his book 'Clinical and Pathological Reports' published in Newry in 1819 [17] it appeared to him "…that the Physician who ascertains half a dozen of important facts, performs a more valuable, though a less splendid achievement, than he who invents a dazzling theory." Samuel Black did truly help develop a dazzling theory - the ischaemic hypothesis of angina pectoris.

A most remarkable feature of Samuel Black's work was that he adopted an epidemiological stance in asking how individuals who become ill differ from those who do not. He put it far more elegantly: "Is our knowledge of the remote causes of this disease such as to enable us to classify the ***liable*** and the ***exempt*?**" (Table **1**). He feared not, but continued "…when we cannot arrive at truth in its perfect and satisfactory form, let us at least endeavour to make approximations towards it. I imagine the persons peculiarly liable are those who are of full and plethoric habits who live luxuriously, or at least very plentifully, and do not use a sufficient quantity of exercise. If there be, on the other hand, any persons possessing an exemption from the disease, total or partial, I think we shall be most likely to find them among the poor, the laborious, those who use strong exercise, the foot-soldier and the female sex." Similarly, he added "We have seen that the disease appears to be connected with a plethoric state of the system and with obesity: - that the great majority of the subjects of it have belonged to better ranks of society, who were in the habit of sitting down every day to a plentiful table, in the pleasures of which they may have indulged to a greater extent than was suitable to the tendency of their constitution," (Samuel Black clearly recognised the genetic component of coronary heart disease).

Table 1. Samuel Black's Classification [17]

The Liable	The Exempt
The old	The young
The male sex	The female sex
The better ranks of society	The poor
The psychologically stressed	The laborious
Those with an ossific diathesis Those with an accumulation of fat around the heart	Those who use strong exercise
Those with full and plethoric habits who live luxuriously	The foot-soldier
Those with insufficient exercise	The French
The obese	

Heberden, Jenner and Parry had noted the disease's predilection for older males, thereby identifying age and gender as the first two risk factors to be established for cardiovascular diseases. Samuel Black observed many more than these and, although the term 'The French Paradox' (a low incidence of coronary heart disease in a country with a relatively high fat consumption) was not to be invented until 1981 [18], he was the first to draw attention to it:

"If the reader should be surprised or confounded by this seeming inadvertence of enlightened British physicians, equally distinguished for industry, zeal and extensive erudition, I beg permission to present to his attentive consideration the following circumstance :—A work has been published in a neighbouring nation, distinguished by the successful cultivation of every department of science, on the diseases of the heart and great vessels : I allude to the " ***Essai sur les maladies du coeur and des gros vaisseaux, par I. N. Corvisart, Paris 1811***." The author, the imperial physician, holding the highest professional rank, was deservedly elevated to a high civil rank also, and the "*Essai"* was ushered into the world under imperial auspices, being dedicated *by permission "* à sa majesté, l'empereur et roi." The work is beyond contradiction one of great merit, and the number of

dissections it contains evinces that the author was in possession of the most ample opportunities of investigation and research. These opportunities have been rendered available by the application of ability, ingenuity and accurate observation. Yet, in this work, such as I have represented it, there is not one word of the disease I have been endeavouring to explain and illustrate. In what light then are we to consider this fact? Can we presume that the author has altogether overlooked or neglected a disease of the heart so serious and important as that under consideration? I can scarcely admit of such a supposition. Shall we then allege that the disease is less known and of less frequent occurrence among our neighbours, than among the inhabitants of these islands? That, I think, is sufficiently probable. I can readily conceive that French habits and modes of living, coinciding with the benignity of their climate and the peculiar character of their moral affections [psychological stress], may have a less tendency to favour this peculiar disorganization than the same circumstances, considered in their application to the inhabitants of the British islands. It is not to be imagined that a disease of the heart, attended with such marked lesion of structure, should be altogether omitted in a work of this kind, if it were of frequent occurrence" [17].

Samuel Black had spotted that not being French was a risk factor for Angina Pectoris.

For treatment of the condition he thought the Physician should "…make himself master of the patient's constitution, of his habits and modes of living." He was "…inclined to propose a regimen of the most abstemious kind, exclusive, in a great measure, of animal food and all fermented drink," but he admitted that "Experience, however, has taught me that it is in vain for men to begin such a system of living, unless they are endowed with a certain firmness and constancy of mind, such as are necessary to enable men to forego Sybaritic gratifications, and to prefer a prospective advantage to a present enjoyment" [17]. Samuel Black well understood that 'habits and modes of living' are resistant to change. As Henry Blackburn observes, "Will-power only lasts a fortnight and dissolves in alcohol."

The concept of 'habits and modes of living' undoubtedly originated with Hippocrates. Samuel Black wrote of Hippocrates' "…acute observation, detailed with a luminous perspicuity and elegant conciseness." The likely source is 'On Airs, Waters and Places' [1]: "…the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and labour, and not given to excess in eating and drinking." Jeaffreson in 1861 records [19] that Louis XV also made the connection between lack of exercise, dietary intake and obesity: laughing at two unwieldy noblemen whose corpulence was the favourite jest of all wits in the court, he said to one of them, "I suppose you take little or no exercise." "Your Majesty will pardon me," replied the bulky Duke, "for I generally walk two or three times round my cousin every morning."

It is of interest that Ancel Keys first used the phrase 'mode of life' in a paper in 1948. Apparently he preferred this to the more modern term 'Lifestyle'. 'Life-style' was first coined by Orgler in 1939 from 'style of life' which Alfred Adler used a decade earlier. Adler adopted the phrase to denote 'a plan of life,' ie a person's consistent movement towards a goal. Over the next years this evolved into the modern meaning of 'lifestyle' ie 'mode of life' [20].

Samuel Black noted that in angina pectoris 'the primary and original cause of the disorder is, perhaps in every instance, the ossification of the coronaries; . . . I have no conception that this ossification is the only link in the chain of causation; but it is the only one we can see clearly' (in fact ossification is a late manifestation of atherosclerosis). Efficient microscopes were not developed until half a century later [21]. As we have seen, both Jenner and Parry had also noted coronary ossification. It was not until well into the 20th century that the concept of ischaemic heart disease came to be generally accepted by the leaders of the medical profession [10].

THE ELUCIDATION OF MYOCARDIAL INFARCTION

By the end of the 19th century the battle against many infectious diseases was being won and life expectancy began to increase resulting in a larger proportion of the population surviving to develop chronic non-communicable diseases. The post mortem findings of coronary thrombosis and myocardial infarction became well-recognised, particularly in Germany, during the second half of the nineteenth century [9]. The clinical syndrome of myocardial infarction in life was first described [22] by an American, James Bryan Herrick, in 1912, however, some hold that the credit for the first description of coronary thrombosis belongs to two Russians, Obratzow and Straschesko, in 1910 [23]. Matthews saw this rivalry as a, "foretaste of the race more than half a century later to put a satellite in orbit" [9]. In 1954, Herrick, who had also described sickle cell disease a year before myocardial infarction, remarked [24] that he, "Did not want to be remembered for the discovery of the 'bizarre' phenomenon of sickle cells but for his description of myocardial infarction." In any case Matthews believed [9] that priority for making the diagnosis in life must go to Doch in 1896 [25]. The disease in the early decades of the twentieth century was still relatively uncommon; Osler reported [26] that of 10,934 admissions to the Montreal General Hospital between 1900 and 1909 there were only six cases diagnosed as angina pectoris. Things were to change: the reporting of the evolutionary electrocardiographic changes of myocardial infarction by Pardee in 1920 made the diagnosis more certain and an epidemic of coronary heart disease began to emerge [27]. This may have been to some extent an example of Graunt's Law (see General Background) as, according to Bedford, the epidemic was due to a, "far greater ability to recognise the disease, thanks to new knowledge and vastly improved means of diagnosis." In addition a sizeable proportion of coronary heart disease in the population may be silent [28] and can only be estimated by population screening. Some authorities maintained that fluctuation in mortality rates was all due to a reclassification of disease [29]. This occurs to an extent routinely with the introduction of fresh revisions of WHO's International Classification of Diseases. This has been considerably augmented with the measurement of troponins in the early 1990s, and what was previously considered to be 'unstable angina' is now recognized as minor myocardial infarction. This has led to the introduction of new definitions of myocardial infarction [30].

THE ADOPTION OF THE POPULATION APPROACH

Credit must go to Sir James Mackenzie (Fig. **1**) for his pioneering work on heart disease. In 1918 at the age of 65 he set up the St Andrew's Institute for Clinical Research in Scotland [31]: "He formulated a scheme for the investigation and prevention of diseases that were common among the people, a scheme to stir up and encourage research into the earliest manifestations of disease." He maintained that such research could, "only be satisfactorily investigated in general practice," as only General Practitioners were in close touch with the patients during the earlier phases of a disease." In the biographical sketch by 'an old friend' at the start of his book, 'The Basis of Vital Activity,' published in 1926, it is consolingly explained [32] that Sir James' "first papers were refused by the leading medical journals, on the grounds presumably of their unorthodoxy. . . He learned the bitter lesson that men are not anxious to be instructed or to be compelled to absorb fresh knowledge," (this may have stimulated him to help found the journal, Heart, in 1909) [33]. Sir James believed that investigators must have the opportunity of, "studying disease in all its varied manifestations from its onset to its termination. . . Thus I decided to start investigations in a community of such a size that individual patients could be watched during the progress of their ill health." A preliminary investigation was made into the forms of ill health that were common among the people and involved a study of the records of 1,000 patients. Thus, Sir James was thinking in terms of the large numbers required for modern epidemiological studies. However, although his views were groundbreaking, they owed more to good medical audit than to non-communicable disease epidemiology. Sir James intended to go further because he wanted to ascertain the 'conditions that predispose to disease' and to study prognosis [34]. Sir James, a sufferer of angina pectoris himself, died suddenly, less than 48 hours after completing his book [32]. Some weeks before his death Mackenzie told Dr (subsequently 'Sir') John Parkinson that he wished him to make a post-mortem examination. After Parkinson had sat with Sir James during his last night, along with Lady Mackenzie, the post-mortem was duly performed some 14 hours after death. This was eventually reported [35] in the first volume of the British Heart Journal in 1939, an indirect successor of Heart, which has now reverted to that title [33]. The post-mortem revealed [35] recent infarction at the apex of the left ventricle and severe atheroma generally.

THE MODERN ERA OF CARDIOVASCULAR STUDIES

Sir James' population approach was to have its followers because in 1926 the Sir James Mackenzie Cardiological Society was formed [36] in his honour in New York. This recognised the fact that Sir James was one of the great pioneers of clinical cardiology of the 20th century. Two years later it changed its name to the New York Cardiological Society; members of this Society were to form the American College of Cardiology in 1949. The President of the Sir James Mackenzie Cardiological Society, Albert S Hyman, had undertaken postgraduate study with Mackenzie, as had Paul Dudley White who, according [37] to Dawber, had: "learnt to share his enthusiasm for a population study of cardiovascular disease."

Apparently White's exposure to Mackenzie was, "undoubtedly responsible for his later practice of keeping careful and detailed records on his own patients and using these data to reach valuable conclusions regarding cardiovascular diseases. . . Later as adviser to Van Slyke at the Heart Institute, White showed a particular interest in the Framingham Study, of which he was one of the major supporters. Commitment at the Institute to the epidemiological approach to cardiovascular disease research was far from universal as many then, as now, believed that the answer to most of the important questions regarding the natural history of atherosclerotic vascular disease would come from basic laboratory research, not from the study of the disease in man."

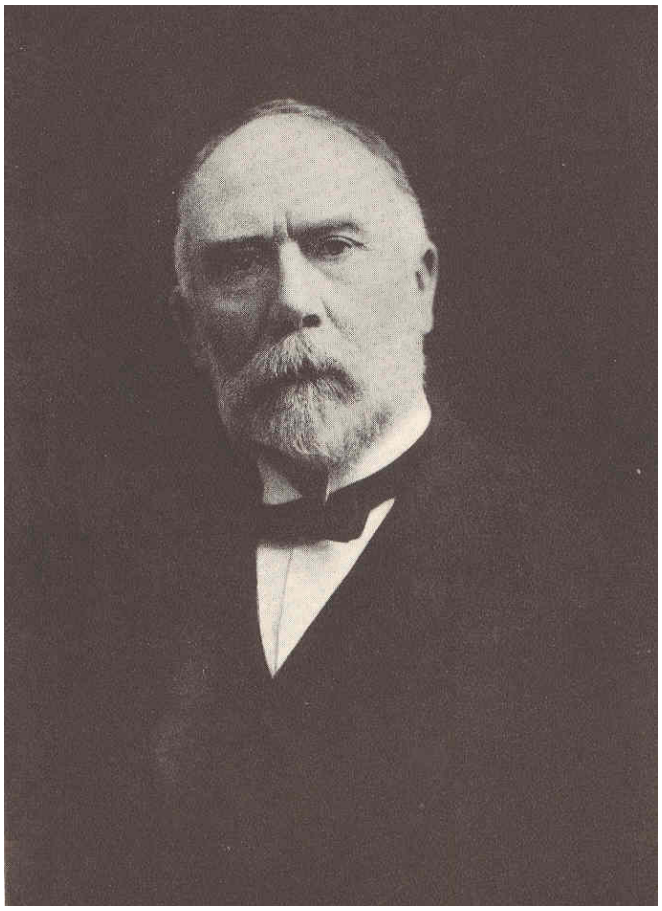

Fig. (1). Sir James Mackenzie 1853-1925.

In any case, thanks to the endorsement of physicians such as White, in 1947 the modern era of the epidemiological study of cardiovascular disease was initiated, with the Framingham Study and a parallel study at Newton, delving into aspects of hygiene [38] (a heart-demonstration program, about which little was subsequently heard). A prospective observational case-control or cohort study was established in just over 5,000 of the town's adult men and women. Framingham was selected because it had been the site for the successful Framingham Community Health and Tuberculosis Demonstration which was established in 1917 [39]. Similarly, three cardiovascular disease studies set up in Norwegian counties from 1974-76 grew out of a tuberculosis eradication programme [40]. It is worth noting in passing, that Norway reported a fall in mortality from circulatory diseases during the war which was ascribed [41] to dietary restrictions, particularly in terms of total

calories through lower fat and cholesterol intake. It would be tempting to describe this as Adolf Hitler's sole contribution to humanity, but changes in death certification brought about by re-employing retired medical staff might have contributed to the pattern observed. As if to illustrate the pitfalls of drawing conclusions from such observational data, a few years later in the same journal, Yudkin in the UK demonstrated [42] a striking association between trends in coronary mortality and the number of radio and television licenses issued.

The redoubtable George Mann stated [43] that, "it was at Framingham that the term 'risk factor' was introduced in a paper in 1957 - a concept borrowed from the world of insurance." The 1957 paper mentions [44] "factors and risk of ASHD" but stops short of using the term 'risk factor'. According to Last *et al.* [45], the term was first used in a Framingham paper in 1961 by Kannel *et al.* [46]. It seems, however, that the term had crept into the medical literature some time before this [47]. In 1981, Hopkins and Williams published [48] 'A survey of 246 suggested coronary risk factors.' Incidentally, there was only one paper cited to justify the measurement of cholesterol in the Framingham Study, but this emerged as one of the classic risk factors, along with smoking and hypertension and a string of lesser factors (male gender and increasing age continued to be important but can be considered as non-preventable). Most of these of course have relevance for other forms of cardiovascular disease. The topic of risk factors in America has been well-aired recently by Oppenheimer [49].

In 1958, the Seven Countries Study was mounted (Fig. **2**) by Ancel Keys of Minnesota [50] and it is a credit to the tenacity of the researchers concerned that both the Framingham and the Seven Countries Studies are still running; now, in addition, studying descendants of the original participants. The yield of these studies was greatly augmented by the introduction of computers which made multivariate analysis possible. Cornfield *et al.*'s paper of 1961 [51] can be seen as groundbreaking in advancing this technique. The influential Seven Countries Study was the first to compare cardiovascular disease incidence and risk factors to a common protocol in different populations, finding large differences in dietary fat intake and also serum cholesterol and heart disease incidence in 13 cohorts in the different countries [52]. A conference had looked at international differences in cardiovascular disease in 1934 [53] and variations within one country were noted in Finland by Kannisto in 1947 [54].

Fig. (2). Seven Countries Study Investigators, Nicotera, Italy 1957. Foreground, left to right: Paul Dudley White, Christ Aravanis, Alfonso Del Vecchio, Ancel Keys (and hangers on).

The Seven Countries Study has spawned a number of books. In his excellent and often humorous account, 'On the trail of heart attacks in seven countries', Henry Blackburn records [55] that Ancel Keys got the idea during a sabbatical year at Oxford, and related travels in 1951 and 1952, which "opened his eyes" to cultural differences in diet, behaviour and disease risk. Blackburn's account stimulates the appetite for such field work. He also makes the point that the Minnesota Business and Professional Men's Study was the pioneer longitudinal epidemiological study of cardiovascular disease and this was also mounted by Keys. Blackburn describes Keys as the 'Patriarch of the Seven Countries Study' and his leadership must have been truly heroic and inspiring to bring the study to fruition. We should all be properly grateful to the Americans for their epidemiological colonialism.

The Seven Countries and other prospective studies developed methodology, questionnaires and validated instruments of measurement for further studies. It was Ancel Keys along with his wife who introduced the concept of 'The Mediterranean Diet' in a cook book [56].

WHO was involved in the Seven Countries Study and it has acted as a catalyst for international epidemiological research. The first edition of the WHO Monograph: Cardiovascular Survey Methods appeared in 1968 [57]; the second in 1982 [58]; and the third in 2004 [59]. It also mounted the WHO MONICA Project to MONItor trends in CArdiovascular diseases [60]. This was established to ascertain to what extent the classic risk factors were driving the diverse trends in cardiovascular mortality reported from different countries. Cross-cultural studies involving subjects who migrated to different countries, such as the NI-HON-SAN Study already existed [61]. MONICA grew out of the 'Decline Conference' which in 1978 had inconclusively discussed the reasons for the fall in coronary heart disease mortality observed in the United States from 1964 onwards [62], and extended to other western countries somewhat later..

Post mortem studies were also carried out, for example from 1960-65 the International Atherosclerosis Project assessed [63] the degree of atherosclerosis of the coronary arteries and aorta in over 31,000 persons in many countries who died aged 10-69 years.

One of the most ambitious studies of all, The National Diet-Heart Study, was never conducted [64]. Although the planning officially began in 1960, from 1956 onwards several investigators individually undertook research programmes which were to be the immediate forerunners of the Study in the United States. Despite further feasibility studies, after two years of deliberation the Executive Committee concluded that a well-controlled mass field trial was needed to test the hypothesis, which was, that alteration of the amount and type of fat and the amount of cholesterol in the diet would decrease incidence of first attacks of clinical coronary heart disease in middle-aged American men. It was "estimated that the study population of up to 100,000 men, with a follow-up period of 4-5 years, would be required to detect a 20% reduction with statistical reliability." The following year the Executive Committee reviewed the accumulated data. A particular cause of concern was the significant drop in serum cholesterol in the control group. Perhaps this was an example of 'contamination' or the 'Hawthorn effect' [65] (where the control group changes its behaviour/risk fac-

tor levels) which has dogged intervention studies, or alternatively, that statistical quirk, 'regression to the mean', may have been playing its part. Work was terminated in May 1965 and the final report appeared in 1968 [64]. It is a source of regret that the study was never conducted as it might have given us an answer to the diet-heart hypothesis which, although we now have important pieces of information, remains to be fully elucidated.

In 1972, the Lipid Research Clinics Program Agreement was signed between the United States and the Soviet Union [66]. It was good to see these two great nations drawing nearer to one another. Israel and Canada were also part of the program. Originally established to mount a series of observational community-based studies, it served as base for mounting the Lipid Research Clinics Coronary Primary Prevention Trial [67].

The above mentioned and countless other studies have brought us to our present level of understanding of cardiovascular epidemiology, but any attempt to cover the vast field is beyond the scope of this brief review. Some, however, deserve special mention: Jerry Morris' physical activity cohort [68] (a cohort study based on London transport and postal workers, and civil servants), the Whitehall Study [69] (a cohort study of London civil servants), the Paris Prospective Study [70] (a cohort study of the Paris police force), The Northwick Park Heart Study [71] (an occupationally based cohort study assessing clotting factors) and other similar studies which, in America, culminated in the United States Cooperative Pooling Project [72].

There were also intervention studies targetted at single risk factors such as blood pressure, eg the Medical Research Council Mild Hypertension Trial [73], or cholesterol, eg the Lipid Research Clinics Trial [74] which demonstrated benefits for cholesterol lowering by means of cholestyramine. In terms of multi-factorial trials WHO deserves a special mention for the European Collaborative Study [75] (multiple cohorts of factory workers in several different European countries), the Americans for the Multiple Risk Factor Intervention Trial [76], and the Finns for the North Karelia Project, a quasi-experimental community-based intervention with a community-based control population [77].

AN EPIDEMIOLOGICAL TRANSITION

There are a number of other important points which deserve to be made. Coronary heart disease mortality has continued to fall in the United States [78], but while cholesterol levels have been falling [79], body mass indices have been increasing alarmingly [80], and other countries are also experiencing this tidal wave of obesity [81]. At the same time as coronary heart disease is decreasing, in western countries at least [82], heart failure is on the increase [83], we are witnessing an 'epidemiological transition' [84] as focal, large coronary artery disease is being supplanted by a more diffuse disease of small vessels in an ageing population.

METHODOLOGICAL ISSUES

As we have seen from the National Diet-Heart Study [64], the necessary steps for designing adequate trials were well known and had been developed long before through the work of Austin Bradford Hill and others [1]. It is therefore surprising that until comparatively recently trials were often of unsatisfactory design and size with problems in the randomisation [85]. We now have the benefit of large meta-analyses which have provided some important guidance. We also have soundly based evidence from trials on, for at least, some of the major cardiovascular disease risk factors. Treating blood pressure is effective therapy, particularly in the prevention of stroke [72]. Cholesterol lowering reduces angiographically assessed atheroma [86], and the five-year incidence of major coronary events, revascularisations and stroke, irrespective of the initial lipid profile or other presenting characteristic [87], without increasing cancer. It is worth noting in passing that in 1819 Samuel Black made [17] this outstanding prediction: "the application of chemical principals. . . may lead to the knowledge of remedies calculated to correct the diathesis, or perhaps to remove the deposit." Why we had to wait so long to show that lowering cholesterol is beneficial, when the deleterious effects of familial hypercholesterolaemia were staring us in the face [88], is hard to justify. We still have no evidence for the benefits of smoking cessation in a randomised setting although Geoffrey Rose nearly managed to conduct such a trial [89].

There has been a proliferation in studies, in the factors which can be measured and, consequently, in risk factors. For example, there is an intriguing hypothesis that our intrauterine nutritional environment determines cardiovascular risk many years afterwards [90]. The concept maintains that adult disease can be ascribed to intrauterine 'programming', but as has been observed, such hypotheses need rigorous testing [91] and that can be methodologically exacting. In any case, such programming is likely to interact with genotype.

CARDIOVASCULAR GENETICS

The emergence of candidate genes for cardiovascular risk has spawned many hypotheses, identifying a host of candidate genes, or new risk factors. Epidemiology has always been good at determining risk in groups of people but less efficient at predicting the outcome in individuals. The 'new genetics' could greatly increase our understanding of why certain individuals are, to employ Samuel Black's unique terminology, liable to the effect of risk factors, while others are exempt [17]. The understanding of gene-environment interactions should greatly refine treatment in the future and explain why the classical risk factors are often imprecise in defining an individual's risk. Rare mutations with big effects are disastrous for the individual, such as familial hypercholesterolaemia [92] but have a small population impact, whereas common polymorphisms with small effects may together produce common diseases and carry a large population impact [93].

The sequencing of the human genome [94] and the genome wide association approach which has stemmed from it, have given us the tools to address these issues, providing that study designs are adequate [95]. The results from genome wide analyses are encouraging [96], but it is unclear how many more false dawns there will be before the many enigmas surrounding cardiovascular disease and its risk factors are resolved.

CONCLUSION

There have been many contributions to cardiovascular epidemiology, but the remarkable insights of Samuel Black, which have lain in obscurity for so long, deserve to be given a wider audience. Steps are currently underway to have his book [17] re-published.

ACKNOWLEDGEMENTS

I wish to record my gratitude to Russell Luepker and Henry Blackburn for their permission to reproduce Fig. (**2**). Thanks are also due to François Cambien, Curtis Ellison, Kari Kuulasmaa, Dan McGee and George Davey Smith for their advice, and to Joe Clint for his relentless pursuit of references. The bones of this review have been published previously [59].

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Received: March 28, 2008 Revised: August 9, 2008 Accepted: August 20, 2008