Q J Med 2012; **105**:509–518
doi:10.1093/qjmed/hcr265 Advance Access Publication 19 January 2012

Review

QJM

An epidemic of coronary heart disease

D.S. GRIMES

From the Department of Medicine, Royal Blackburn Hospital, Haslingden Road, Blackburn, Lancs BB2 3HH, UK

Address correspondence to Dr D.S. Grimes, Department of Medicine, Royal Blackburn Hospital, Haslingden Road, Blackburn, Lancs BB2 3HH, UK. Email: davidgrimes1@mac.com

Introduction

The major public health concern during the past 50 years has been coronary heart disease (CHD), which has been the leading cause of death in the UK and other nations in the temperate parts of the world, in particular northern Europe and North America. It has run in families and it has brought to a premature end the lives of people in their prime. It has robbed wives of their husbands and husbands of their wives. It has robbed children of their parents and sometimes parents of their children.

However, it is now clear that in these countries CHD was an epidemic of the latter half of the 20th century. The onset of the epidemic appears to have been shortly after the First World War, but now, in the early 21st century, the epidemic is almost at an end.

The early recognition of CHD

The earliest clinico-pathological report of CHD was in 1859, an anecdotal case report of myocardial infarction (MI) presented to the Swedish Medical Society.[1] It defined the clinical features of MI and also the pathological features found at autopsy, linking the two aspects. The report was not known outside Sweden and at the time it did not appear to be important. The fact that this was a single case report was emphasized by the Swedish physician B.W. Johansson and pathologist P. Nichol. They drew attention to the 1859 report, contrasting it with 770 new cases of MI occurring in Malmo in 1978 alone.[1]

At the beginning of the 20th century, CHD was effectively unknown in the UK. It received no mention in the earlier writings of Sir James MacKenzie, who was initially a general medical practitioner in Burnley, Lancashire and later the father of cardiology in the UK.[2] MacKenzie first mentioned angina in the third edition of his book *Diseases of the Heart* published in 1913,[3] but he did not relate in to disease of the coronary arteries. By 1923, he was able to write a book entitled *Angina Pectoris*,[4] indicating that by this time the condition had appeared in clinical practice.

Sir William Osler was the most influential physician and medical teacher of the late 19th and early 20th centuries. His *Principles and Practice of Medicine*, the first textbook of medicine, was first published in 1895 and there was no mention of angina. In the 1912 edition he wrote: 'It [angina] is a rare disease in hospitals: a case a month is the average even in the larger metropolitan hospitals.'[5]

We know that physicians of this era had exceptional clinical skills and powers of observation. They described a wide range of clinical syndromes, many of which bear their names to this day. They laid the foundations of descriptive clinical and medical taxonomy. They also laid the foundations of pathology and of clinico-pathological correlation. If they did not recognize the characteristic features of CHD that we have been accustomed to in clinical medicine, and indeed in everyday life, during the latter half of the 20th century, then it could not have existed.

In the early years of the 20th century, the major forms of heart disease were the late results of rheumatic fever and syphilis, and also endocarditis, all of which are caused by micro-organisms and for which penicillin later became an effective treatment.

The medical condition of MI due to disease of the coronary arteries was first suggested in the USA in 1912, the initial publication by Herrick,[6] but a decade later in the UK after two more of his articles appeared.[7,8] By the 1930s and 40s, CHD was widely recognized and CHD was included in the International Classification of Disease (ICD) after 1930.

The emergence of the epidemic

The important 1963 review by Dr Maurice Campbell of Guy's Hospital took data from the Registrar-General's Statistical Reviews of England and Wales, acknowledging advice from Sir Austin Bradford Hill, and it gives us a great insight into the emergence of CHD.[9] He felt that from 1876 (the earliest public records) until 1921 the death rate from diseases of the heart in general changed very little, and there was no specific mention of CHD. However, the death rate from diseases of the heart started to increase during the years 1922–24 and this would appear to have been the onset of the epidemic. The death rate from CHD in England and Wales increased from 2.9/100 000 in 1921 to 16.6/100 000 in 1931. The recorded deaths from cerebrovascular disease also increased, fewer but by the same factor as CHD. Campbell commented about the increase of CHD deaths after 1921 that 'the death rate had doubled by 1927, doubled again by 1929, again by 1933, again by 1939, again by 1948, and again for the sixth time by 1956'. He noted this to be a geometric increase, a characteristic of biological growth. Campbell discussed the possibility that the increase might be due to a change in fashion, a change in the nomenclature of disease. However, he excluded the increase being just a name change because the total number of deaths from heart disease was increasing during these years, which obviously indicated that something new was happening, even if not fully understood at the time. It is only after a new disease becomes established that we name and record it accurately, and we saw this with the more recent AIDS epidemic. It was only after 1940 that deaths from rheumatic and syphilitic heart disease were in decline.

Deaths from CHD were very obvious by the 1950s, and in the post-war years were becoming a public health concern. The UK death rate in 1950 was 200/100 000 population, about twice the death rate from tuberculosis, and it more than doubled during the next decade. The peak incidence was reached in 1970, at 550 deaths per 100 000 population[10] (Figure 1). For men aged 55–64 years in England and Wales, the mortality rate from CHD reached, in 1972, a peak of 730/100 000 and in Scotland 960/100 000.[11] There was now a major public health challenge, and the hospitals were responding to the increased number of admissions. During the late 1960s and early 1970s, coronary care units were opened and cardio-pulmonary resuscitation (CPR) was developed.

One view of the epidemic of CHD is that it could have been unmasked by the fact that people were no longer dying at a younger age from infectious diseases, as discussed in a second paper by Campbell.[12] However, the emergence of CHD and

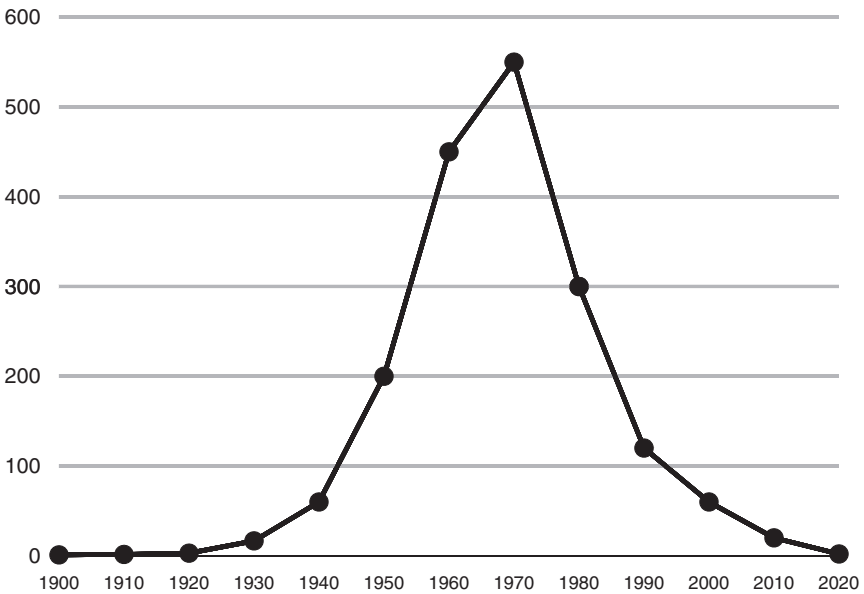

Figure 1. Deaths in UK from CHD per 100 000 (age standardized). Before 1950 England & Wales; 1950 onwards UK data.[9,10,25,26]

the rapid mortality increase between 1922 and 1950 could not have been the result of antibiotic therapy eradicating obvious microbial diseases. The emergence of the epidemic in the USA coincided with an increase between 1900 and 1968 of both the total population (from 76 to 200 million) and also average life expectancy (from 47.3 years to 70.2 years).[13] On the basis that 90% of CHD deaths occurred after the age of 55 years, it was suggested that increased longevity was the cause of a spurious epidemic.[14] Or perhaps, the perceived epidemic was a reflection of changes in diagnostic and coding practice rather than disease change, again discussed but rejected by Campbell[9] and also in considerable detail by Robb-Smith[15] Another view expressed was that CHD had always been present but unnoticed by the physicians and pathologists of the early 20th century, that atherosclerosis was 'ubiquitous' and that an epidemic of CHD was 'impossible'.[16]

Tuberculosis had been a major cause of death during the first half of the 20th century. The death rate in men was 110/100 000 in 1950, falling to 32 in 20 years later during which time-specific antimicrobial treatment was introduced.[17] Therefore, 80 men per 100 000 per year did not die from tuberculosis during the two decades leading to the peak incidence of CHD deaths. This does not explain why by 1970, the death rate from CHD reached 550/100 000.

The most popular explanation was and still is a lifestyle factor change, especially increasing affluence and food consumption, but these thoughts are not correct and they do not stand up to evidence. Most obviously, the affluence of the UK, the USA and European populations increased dramatically not during the years 1920–70, but after 1970, when the peak of CHD was reached and a rapid decline of deaths had commenced. It must be remembered above all that in the UK, USA and northern Europe, it is the poorest people and the long-term unemployed who have had by far the greatest risk of CHD and early death.[18,19] The affluent have enjoyed the best health and the lowest risk of death from CHD.[20]

The decline of the epidemic

The decline in deaths from CHD in men and in women was clearly documented in the UK and in the USA, the peak being passed earlier in the USA (1960) than in the UK (1970).[10] It was not just CHD that was in rapid decline. There was a major reduction of age-adjusted stroke deaths during a similar time period, but starting off earlier in about 1950 in the USA and in about 1960 in the UK. During the following 30 years, the stroke mortality fell by ~60%.[21] It has continued to fall in north-western European nations, by ~50% of 1980 incidence to an average of about 100 deaths per 100 000 population at the present time, with further decline anticipated.[22]

The decline of deaths from CHD became obvious, but not the reason for it.[23] The 1978 Bethesda Conference was convened to address the decline, and as a result the World Health Organisation set up the MONICA project *Monitoring Trends and Determinants in Cardiovascular Disease.* The stated objectives of the study were to validate the decline in deaths from CHD in a variety of countries where this was possible, and to determine the reasons, whether the result of a reduction of coronary events or an improved survival from such events.[24]

The decline of CHD deaths in the UK was further described in a UK Government report of 2004, *Winning the War on Heart Disease*.[25] In this report, the government predictably but undeservedly assumed responsibility for the decline. Clearly, the NHS in the UK could not have had an international effect.

The government report presented the decline of mortality from CHD in graphical form (Figure 2). The displayed data started in 1990 when the mortality rate had already fallen dramatically by >80–90% per 100 000 men and 25/100 000 women. The decline of heart disease was progressive from then until 2003, and this was obviously good news for which the government of the day took the credit. *Winning the War on Heart Disease* extrapolated the findings to indicate that age-standardized deaths from CHD would come to an end in 2013 in women and in 2016 in men. Although extrapolation is always suspected, it has proved to be justified. The downward trend continued to 2007: we remain on track for the end of deaths from CHD in 2013–16[26] (Figure 3).

The European experience

The mortality rate from CHD has declined in all European countries as well as in the USA. It is in the countries with high incidence that the greatest decline has occurred, for example a reduction of MI by ~80% in the UK, Slovakia, Netherlands and Ireland. The decline has been least at 30% in Portugal and Greece, which is hardly surprising as the incidence of MI and deaths from CHD have been low in Mediterranean countries. There was a wide variation of CHD death rates within Europe, but they are now remarkably similar with MI

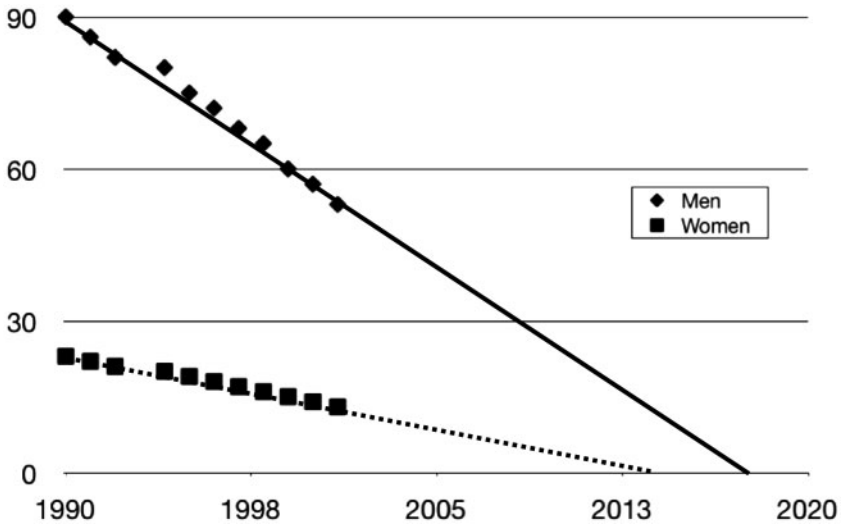

Figure 2. Projected decline of coronary heart disease. Winning the War on Heart Disease, UK Government 2004.[14]

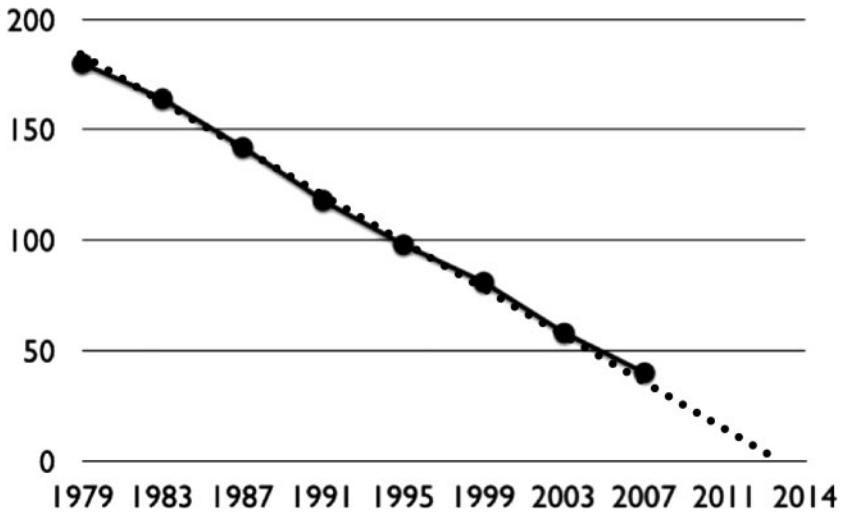

Figure 3. UK: death rate from CHD per 100 000 (age standardized). From Appleby J, 2011.[18]

incidence (not death rates) ~40/100 000/annum.[26] Further decline can be expected as predicted for the UK and France. It is important to note that the pattern of CHD and its decline is not a characteristic of any specific country.

The impact of medical interventions

An important aspect of the decline of mortality rates is to identify the effects of medical intervention. In particular, we need to identify the statin effect as statins are used extensively for primary prevention, revascularization usually being used after an initial cardiac event.

The first trial of statin therapy was published in 1994, the 4S trial (Scandinavian Simvastatin Survival Study).[27] Although previous studies had shown that statins reduce the cholesterol level of the blood, this was the first to show a clinical benefit in respect of survival. It was a secondary prevention trial and thus recruited high-risk individuals who had already experienced a cardiac event.

This was followed in 1995 by the first primary prevention trial, WOSCOPS, which was based in the west of Scotland and was a 5-year study of men aged between 60 and 65 years at the time of recruitment.[28] These men would have had the world's highest risk of death from CHD.

However, the death rate from CHD had already fallen by ~90% by the time these publications appeared, and therefore before the widespread use of statins. The trend-line of decline of CHD deaths in the UK did not display any subsequent

deflection (see figures) and there was no obvious effect of statin therapy or other medical intervention.

We tend to overestimate the benefits of medical intervention, and the reason for this is that not all patients benefit from that treatment. The clinical trial of thrombolysis therapy for MI published in 1988 [Second International Study of Infarct Survival (ISIS-2)] tells us that a combination of aspirin and streptokinase benefits only 5 out of 100 patients treated; number needed to treat (NNT) equals 20, a vascular mortality reduction from 13.2% in the control group to 8% in those treated.[29] Secondary prevention with simvastatin (the 4S trial[27]) shows only 2 out of 100 not dying as a result of treatment; NNT of 50. In the primary prevention trial WOSCOPS,[28] the mortality reduction in the pravastatin-treated group was 3.1% compared to 4.2% in controls, 1 in 100 not dying, a survival NNT of 100. We assume that all patients treated benefit from treatment but this is far from reality.

There is now need for a re-evaluation of primary prevention. Recruitment to WOSCOPS was in about 1986, when the UK average death rate was ~250/100 000, about 10 times greater than now. So today the estimated NNT would be about 1000. In the south-east of England coronary deaths have been about half those in the west of Scotland, and so in the south-east of England the NNT would now be 2000. For younger men aged ~50 years, the NNT would rise to about 4000. For women of similar age, it would need to be multiplied by 3 to 12 000. The appropriateness of giving a medicine (not without side-effects) to 4000 men or 12 000 women for 5 years to prevent one death is a matter of judgement. It looks as though after 2016 it will be pointless.

Medical intervention was not the reason for the end of the epidemic of CHD. The conclusion of the MONICA projected as published in 1999 suggested that the main determinant of the decline of CHD mortality was 'whatever drives changing coronary-event rates'.[30] The implication is that we have perhaps experienced the natural decline of a natural epidemic, but observations of the rapid decline of deaths from CHD generally ignore completely the development of the epidemic in the first half of the 20th century.

The effects of the end of the epidemic

Although clearly displayed in *Winning the War on Heart Disease,* a widely circulated government report with good media coverage, the point about the end of CHD does not appear to have been absorbed by the media, by the population, by the medical profession, nor by the government. The end of the epidemic of CHD would inevitably have several major impacts, on the basis that many people will now be living much longer.

The first effect is that we might expect to see an increase in cancer deaths, occurring in those who would previously have died from CHD. However, between 1999 and 2009, the death rates from cancer in England and Wales have fallen, by 15% for males and 12% for females. The absolute death rates are (in 2009) 208/100 000 for males and 131 for females,[31] whereas at the peak of its epidemic CHD was responsible for almost three times this rate of deaths.

It is inevitable that we are going to have more very old people and many more people living to the age of 100. There were 2600 centenarians in the UK in 1981, increasing to 11 600 in 2009. The estimate is about 80 000 in 2033.[32] This increase is having a large impact on community services and hospital admissions as more people are living into old age and are experiencing the general infirmities associated with it.

It is also having an effect on pension funds, which are no longer able to sustain previous levels of pensions for so many people, whose lives are now extended by an average of 10 or more years compared to 20–30 years ago. The days are almost over when a man might work and pay his pension contributions until the age of 65 years only to die from a heart attack 6 months after retirement. His pension might now need to continue for 25 years or even longer.

The number of people not dying from CHD has been increasing progressively during the time that the mortality rate has been decreasing, since 1970. Each year, a population of 100 000 will now have an additional 500 people living into an older age. Cumulatively, this would be 5000 during the last decade, 3 million nationally. The total for the years since 1970 would be about 15 000, which would be 9 million nationally. Clearly, many of these would have died by now, but at an older age and almost certainly with greater infirmity.

These factors could have been predicted in 1990, knowing that by that year the number of deaths from CHD had fallen by >80%.

Paradoxes

The decline of CHD creates certain paradoxes in respect of existing understanding of the nature and cause of the disease. Paradoxes are obviously uncomfortable to those in persist in maintaining the

present incorrect view of CHD, that it has always been present, that it is due to faulty living and eating, or that is genetic. However, paradoxes are very important in identifying errors in understanding and therefore giving a stimulus to updating our view of the world. Let us look at a clinical example.

I recently saw in the outpatient clinic a 65-year-old man of south Asian ethnicity on account of non-alcoholic fatty liver disease, the pointer being a mildly abnormal liver enzyme test (ALT) and also characteristic ultrasound scan appearances. He was already known to have type 2 diabetes, hypertension, hypercholesterolaemia and asthma; until recently, he smoked cigarettes. A few months earlier, he had been admitted to hospital as an emergency on account of chest pain, and there was every expectation at that time that he was suffering from MI. ECG's and troponin turned out to be normal, but because the probability of CHD was thought to be very high, coronary angiography was performed. The coronary arteries turned out to be normal with no evidence of CHD.

On existing understanding of CHD, the outcome should not have been normal coronary arteries: existing understanding is clearly incorrect. This is a single case but not unique, an example, of a major change that is taking place in clinical medicine in the UK. Coronary care units are gradually changing their function. The need for post-MI temporary pacemakers has reduced in a major way, and the need for heart transplantation has also reduced. Hospital resuscitation teams are perhaps inappropriately turning their attention from post-MI cardiac arrest to the end of life of the very elderly, and we have a new need for 'Do Not Resuscitate' orders.

Cholesterol

In Europe, we can now stop worrying about cholesterol. Our present-day concern about cholesterol stems from the finding of cholesterol in the wall of atherosclerotic coronary arteries and also the observation that a high blood level of cholesterol is predictive of death from CHD. But this is true only in young men,[33] and in older people high cholesterol levels give a survival advantage.[34–36] There are many associations between a high blood cholesterol and protection against ill-health, for example HIV infection,[37] hospital admission and death from respiratory disease,[38] post-operative abdominal infection,[39] cancer development,[40] disability following stroke.[41]

The main point is that the only disadvantage of high blood cholesterol is its association with premature death from CHD. With the end of the epidemic of CHD, the only disadvantage of a high cholesterol level is no longer present. It has been stated that the 'Polypill' (aspirin, lisinopril, hydrochlorothiazide, simvastatin) halves cardiovascular risk.[42] This is based not on measurement of the end-point of cardiovascular events and death, but on risk factor reduction,[43] no longer relevant as deaths from CHD are now so low. Research has been based on out-of-date risk predictions.

The present wide-spread primary care activity to test for and 'treat' high blood cholesterol needs to be reviewed. The CHD prediction algorithms certainly need to be brought up-to-date as they are causing unnecessary worry to many people by seriously exaggerating risk. Present-day predictions are based on historic data, mainly on Framingham data from cohorts born in the first half of the 20th century.[44] With our knowledge that childhood factors are very important in the subsequent development of CHD,[45–47] predictions based on these data are of doubtful relevance to people born in the second half of the 20th century. CHD prediction tables are still being generated using historic data,[48] but with the end of the epidemic of CHD, perhaps they should be withdrawn.

Other risk indicators

CHD is a specific disease and it is not just an accumulation of risk factors. This is shown very well by the clinical example, a man who had a full set of risk factors, but normal coronary arteries.

We are now in the 21st century and the epidemic of CHD is close to its end, but nevertheless risk factors continue. We are told that the alleged epidemic of obesity will lead to an epidemic of CHD, but this is not true. The epidemic of CHD is already almost over, and the decline was at the time when the prevalence of obesity was apparently increasing.

Public health attention to risk factors such as blood pressure control will have been of limited help in the decline of the epidemic, but an explanation of the decline must also explain the emergence of the epidemic. The initial placebo controlled trials of the treatment of hypertension (favourable and therefore not to be repeated) indicate a significant reduction of deaths from stroke, renal failure and heart failure, but a very marginal reduction of deaths from CHD.[49] High blood pressure and its control could not have made a major impact on the emergence or decline of the epidemic of CHD.

Commentators on the decline of CHD tend to look at a very restricted timescale, just a snap-shot of an almost century-long process. The assumption is that CHD has always been present, and therefore

that any decline must be the result of medical intervention, greater control of risk factors. A recent report from the US Centres for Disease Control and Prevention noted a 6–6.7% decline of age-adjusted CHD prevalence in the USA between the years 2006–10, attributing this to risk factor reduction.[50] This leads to renewed efforts to target children for lipid screening and life-long statin therapy among other things.[51] The cost of this would be enormous and if in the UK, the benefit would be non-existent.

Reflections on causation

It is important to recognize that CHD with underlying atherosclerosis is a specific disease, with specific pathological features and it will have a specific cause. This is the fundamental message of the medical scientific philosopher Paracelsus, but his message tends to have been lost in respect of CHD. Many, if not most people seem to think that it has different causes in different people. In some, it is said to be due to a faulty diet, in some faulty genes, in others working too hard and in others being unemployed. Stress, diet, cigarettes, genetics are the usual culprits but none stands up to scrutiny.

It is important to recognize that CHD in Europe and North America has been an epidemic, the cause of which remains a mystery and at present we can only speculate. If we look at medical history, we find that all epidemics come to an end, usually for reasons that are not clear. It is still claimed that CHD is due to genetic factors,[52] but it is obvious that an epidemic cannot be due to faulty genes, which have a stable prevalence over a long period of time. However, genes can have an influence on susceptibility, as shown by a large family with hypercholesterolaemia. The family members had a very significant health advantage recorded in the 19th century [Standardised Mortality Ratio (SMR) 70 for men, 40 for women], but they developed a distinct disadvantage during the years of the epidemic of CHD (1960 peak SMR 180 for both sexes).[53] Their high level of expression of cholesterol in the inflammatory process might have had certain advantages in the 19th century, but distinct disadvantages during the 20th century in the presence of CHD, in which the inflammation is within the arterial wall and thus narrows its lumen.[54]

The diet–cholesterol–heart hypothesis has been dominant during the past 50 years, with implications for nutritional and pharmaceutical industries. It has, however, stifled other aspects of thinking and research,[55] especially with the introduction of statins. There is no doubt that this class of drugs has significant benefit in CHD, but to equate this with cholesterol lowering indicates faulty scientific thinking.[56] Ezetimibe, a medication that powerfully reduces blood levels of cholesterol has no demonstrated clinical benefit.[57,58] Statins have effects beyond cholesterol lowering, effects that appear to be of widespread and fundamental importance in a variety of illnesses and pathological processes.[59] These include both inflammatory and malignant processes,[60] but even these are almost stifled by the mistaken obsession with cholesterol.

The time sequence, magnitude and widespread nature of the epidemic of CHD indicate that it could not realistically have been due to behavioural factors or dietary factors. There has clearly been an environmental factor. In theory, it could have been a physical, chemical or biological factor. There is no evidence of a physical factor, and there is no consistent evidence of chemical poisoning, even dietary. Cholesterol cannot explain the epidemic. It was almost certainly a biological factor, as has been the case with other epidemics.

The epidemic is now virtually at an end, but we are left with the question, has CHD been due to an environmental biological factor, which is a micro-organism, a bacterium or a virus? If so, it has not been clearly identified, but it has never been fully investigated. *Chlamydia pneumonia* has been a culprit micro-organism, but research has been inconclusive.[61–64] The failure to identify a specific micro-organism does not invalidate the likelihood that CHD is due to a chronic infection, and Koch himself was aware that his postulates, with high specificity but low sensitivity, would 'rule in' but could not 'rule out' a putative causal micro-organism. The earlier major causes of heart disease (syphilis, rheumatic fever, endocarditis) were due to micro-organisms but initially obscure in causation. Ninety per cent of the cells that constitute the human adult are micro-organisms, the vast majority of which cannot yet be identified. We must remember that these are mainly inherited, especially from the mother, and these micro-organisms carry up to 3 million genes, compared to our 25 000 human genes.[65] Microbiology can be said to be still in its infancy, and so is genetics.

Implications for the rest of the world

During the 20th century, the epidemic of CHD was effectively confined to the relatively affluent nations of Europe, North America, Australia and New Zealand. However, with the end of the epidemic in these countries, it appears that in the 21st century similar epidemics are emerging in the newly

industrializing and other 'non-western' countries, in particular Latin America, the Middle East and urban India, with stroke having a higher incidence in China, Southeast Asia and sub-Saharan Africa.[66] Although these new epidemics are assumed to be due to life-style changes and 'affluence' this may not be correct, and of course history tells us of epidemics of known microbiological causation can spread between continents. It would not be expected for an epidemic of such worldwide distribution to be caused by behavioural or dietary factors. The dietary policies of the United Nations to prevent cardiovascular disease might be unfounded.[67] If the epidemic of CHD in the western world were indeed the result of a micro-organism, then the decline of the epidemic is likely to be the result of the development of herd immunity, as is the case with the decline of other epidemics.

There are predictions of a 'tsunami' of CHD in low- and middle-income countries, based not on observations of disease incidence but on 'risk factors', especially an increase in population-average BMI, blood pressure and cholesterol, although there are several inconsistencies.[68] Industry and atmospheric pollution will cause their own problems, but on the basis of experience in the previously industrialized countries the rise and fall of an epidemic of CHD cannot be explained on the emergence and regression of known risk factors.

If we learn from the epidemic of CHD in Europe and North America in the 20th century, acknowledging that its emergence and decline are not explained, then a renewed search for a microbiological agent might lead to an effective way of stopping further epidemics in the 21st century before their natural sequences cause very large numbers of premature deaths.

Conflict of interest: None declared.

References

1. Johanss BW, Nicol PA. Swedish report on acute myocardial infarction in 1859. *BMJ* 1982; **284**:888–9.
2. Wales AE, Shafer J. *Sir James MacKenzie: the Burnley years*. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1033731/pdf/medhist00146-0091.pdf (4 January 2012, date last accessed).
3. MacKenzie J. *Diseases of the Heart*. London, Oxford University Press, Hodder & Stoughton, 1913.
4. MacKenzie J. *Angina Pectoris*. London, Henry Frowde, Hodder & Stoughton, 1923.
5. Osler W. *Principles and Practice of Medicine*. London, Appleton, 1912:836.
6. Herrick JB. Clinical features of sudden obstruction of the coronary arteries. *JAMA* 1912; **59**:2015–20.
7. Herrick JB, Nuzum FR. Angina pectoris: clinical experience with two hundred cases. *JAMA* 1918; **10**:67–70.
8. Herrick JB. Thrombosis of the coronary arteries. *JAMA* 1919; **72**:387–90.
9. Campbell M. Death rates from diseases of the heart: 1876 to 1959. *BMJ* 1963; **ii**:528–35.
10. Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation* 2004; **109**:1101–7.
11. Florey C de V, Melia RJW, Darby SC. Changing mortality from ischaemic heart disease in Great Britain 1968-76. *BMJ* 1978; **1**:635–7.
12. Campbell M. The main cause of increased death rate from diseases of the heart: 1920-1959. *BMJ* 1963; **ii**:712–7.
13. US Department of Commerce 1980. Statistical abstract of the United States 1980. Washington DC, US Government Printing Office, 1980(As quoted by Stehbens WE. The hypothetical epidemic of coronary heart disease and atherosclerosis. *Medical Hypotheses* 1995; 45:449-54 [14]).
14. Stehbens WE. The hypothetical epidemic of coronary heart disease and atherosclerosis. *Medical Hypotheses* 1995; **45**:449–54.
15. Robb-Smith AHT. *The Enigma of Coronary Heart Disease*. London, Lloyd-Luke, 1967.
16. Stehbens WE. An appraisal of the epidemic rise of coronary heart disease and its decline. *Lancet* 1987; **329**:606–10.
17. Springett VH. Tuberculosis - epidemiology in England and Wales. *BMJ* 1972; **1**:422–3.
18. Macintyre K, Stewart S, Chalmers J, Pell J, Finlayson A, Boyd J, *et al*. Relation between socioeconomic deprivation and death from first myocardial infarction in Scotland: population based analysis. *BMJ* 2001; **322**:1152–3.
19. Barakat K, Stevenson S, Wilkinson P, Suliman A, Ranjadayalan K, Timmis AD. Socioeconomic differentials in recurrent ischaemia and CHD mortality after acute myocardial infarction. *Heart* 2001; **85**:390–94.
20. Marmot MG, Shipley MJ, Rose G. Inequalities in death: specific explanations of a general pattern? *Lancet* 1984; **323**:1003–6.
21. Stamler J. The marked decline in coronary heart disease mortality rates in the United States, 1968-1981; summary of findings and possible explanations. *Cardiology* 1985; **72**:11–22.
22. Kunst AE, Amiri M, Janssen F. The decline in stroke mortality. Exploration of future trends in 7 western European countries. *Stroke* 2011; **42**:2126–30.
23. National Institutes of Health. *National Conference on Health Research Principles, 3 an 4 October, 1978: conference report*. Bethesda, Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, 1978.
24. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakanyas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA project. *Circulation* 1994; **90**:582–612.
25. UK Department of Health. *The National Service Framework for Coronary Heart Disease: Winning the War on Heart Disease*. London, The Stationary Office, 2004.
26. Appleby J. Does poor health justify NHS reform? *Brit Med J* 2011; **342**:10(d566).

27. Scandinavian Simvastatin Survival Study Group. Randomised controlled trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**:1383–9.
28. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, *et al.* for the West of Scotland Coronary Prevention Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolaemia. *N Engl J Med* 1995; **333**:1301–7.
29. Second International Study of Infarct Survival Collaborative Group. Randomised Trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **332**:349–60.
30. Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. *Lancet* 1999; **353**:1547–57.
31. Office for National Statistics. Births and Deaths in England and Wales 2009. Statistical Bulletin. UK Government; 21 July 2010. Crown Copyright.
32. Office for National Statistics. Centenarians: number of centenarians grows. Population estimates for UK, England and Wales, Scotland and Northern Ireland. UK Government; 30 September 2010. Crown Copyright.
33. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality: 30 years of follow-up from the Framingham study. *JAMA* 1987; **257**:2176–80.
34. Forette B, Tortrat D, Wolmark Y. Cholesterol as risk factor for mortality in elderly women. *Lancet* 1989; **333**: 868–70.
35. Krumholtz HM, Seeman TE, Merrill SS, Mendes de Leon CF, Vaccarino V, Silverman DI, *et al.* Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA* 1994; **272**:1335–40.
36. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet* 2001; **358**:351–55.
37. Claxton AJ, Jacobs DR Jr, Iribarren C, Welles SL, Sidney S, Feingold KR. Association between serum total cholesterol and HIV infection in a high-risk cohort of young men. *Journal of Acquired Immunodeficiency Syndromes and Human Retrovirology* 1998; **17**:51–7.
38. Iribarren C, Jacobs DR Jr, Sidney S, Claxton AJ, Gross MD, Sadler M, *et al.* Serum total cholesterol and risk of hospitalization, and death from respiratory disease. *Int J Epidemiol* 1997; **26**:1191–202.
39. Pacelli F, Doglietto GB, Alfieri S, Piccioni E, Sgaradi A, Gui D, *et al.* Prognosis in intra-abdominal infections. Multivariate analysis on 604 patients. *Arch Surg* 1996; **131**:641–45.
40. Rose G, Blackburn H, Keys A, Taylor HL, Kanel WB, Paul O, *et al.* Colon cancer and cholesterol. *Lancet* 1974; **1**:181–83.
41. Dyker AG, Weir CJ, Lees KR. Influence of cholesterol on survival after stroke: retrospective study. *BMJ* 1997; **314**:1584–8.
42. Mayor S. Four in one polypill halves predicted cardiovascular risk, international study shows. *BMJ* 2011; **342**:1229 (d3355).
43. PILL Collaborative Group. An international randomised placebo-controlled trial of a four-component combination pill (''Polypill'') in people with raised cardiovascular risk. *PLoS ONE* 2011; **6**5e19857.
44. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med* 2011; **365**:213–21.
45. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *Br J Prevent Social Med* 1977; **31**:91–95.
46. Barker DJP, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986; **327**:1077–81.
47. Kaplan GA, Salonen JT. Socioeconomic conditions in childhood and ischaemic heart disease during middle age. *BMJ* 1990; **301**:1121–23.
48. Norheim O, Gjelsvik B, Klemsdal TO, Madsen S, Meland E, Narvesen S, *et al.* Norway's new principles for primary prevention of cardiovascular disease: age differentiated risk thresholds. *BMJ* 2011; **343**:132–35 (d3626).
49. Veterans Administration Cooperative Study on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. *JAMA* 1970; **213**:1143–52.
50. Centers for Disease Control and Prevention: *Morbidity and Mortality Weekly Report* 2011; 60: 1377-81. Reported by Fang J, Shaw KM, Keenan NL. *JAMA* 2011; **306**:2084–86.
51. http://www.nhlbi.nih.gov/guidelines/cvd_ped/ Reported in *The Lancet* 2011; 378:1826.
52. Sundquist K, Winkleby J, Li X, Ji J, Hemmenki K, Sundquist J. Familiar transmission of coronary heart disease: a cohort study of 80,214 Swedish adoptees linked to their biological and adoptive parents. *Am Heart J* 2011; **162**:317–23.
53. Sijbrands EJG, Westendorp RGJ, Defesche JC, de Meier PHEM, Smelt AHM, Kastelstein JJP. Mortality over two centuries in a large pedigree with familial hypercholesterolaemia: family tree mortality study. *Brit Med J* 2001; **322**:119–23.
54. Ravnskov U, McCully KS. Vulnerable plaque formation from obstruction of *vas vasorum* by homocysteinylated and oxidized lipoprotein aggregates complexed with microbial remnants and LDL autoantibodies. *Ann Cli Lab Science* 2009; **39**:3–16.
55. Adams DD. The great cholesterol myth; unfortunate consequences of Brown and Goldstein's mistake. *QJM* 2011; **104**:867–70.
56. Grimes DS. History of the cholesterol hypothesis in Britain. *QJM* 2009; **102**:436–8.
57. Kastelein JJP, Akdim F, Stroes ESG, Zwinderman AH, Bots ML, Stalenhoef AF, *et al.* Simvastatin with or without ezetimibe in familial hypercholesterolaemia. *N Engl J Med* 2008; **358**:1431–43.
58. Mascitelli L, Pezzetta F, Goldstein MR. Role of ezetimibe in the prevention of cardiovascular disease: absence of evidence. *Arch Med Res.* 2010; **41**:649–50.
59. Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. *Lancet* 1996; **348**:1079–82.

60. Kodach LL, Jacobs RJ, Voorneveld PW, Wildenberg ME, Verspaget HW, van Wezel T, *et al*. Statins augment the chemosensitivity of colorectal cancer cells inducing epigenetic reprogramming an reducing colorectal cancer cell 'stemness' via the bone morphogenetic protein pathway. *GUT* 2011; **60**:1544–53.

61. Benditt EP, McDougall JK. Viruses and vascular disease. *Cardiology in Practice* 1989; **7**:34–39.

62. Cunningham MJ, Pasternak RC. The potential of viruses in the pathogenesis of atherosclerosis. *Circulation* 1988; **77**:964–66.

63. Saikku P, Leinonen M, Mattila K, Ekma M-R, Nieminen MS, Mäkelä PH, *et al*. Serological evidence of an association of a novel Chlamydia, TWAR, with chronic coronary heart disease and myocardial infarction. *Lancet* 1988; **332**: 983–85.

64. Taylor-Robinson D, Thomas BJ. *Chlamydia pneumoniae* in arteries: the facts, their interpretation, and future studies. *J Clin Path* 1998; **51**:793–97.

65. Ainsworth C. I am legion. *New Scientist* 2011; **210**:43–5.

66. Reddy KS. Cardiovascular disease in non-western countries. *N Eng J Med* 2004; **350**:2438–40.

67. Mozaffarian D, Capewell S. UN's dietary policies to prevent cardiovascular disease. *BMJ* 2011; **343**:546(d5747).

68. Anand SS, Yusuf S. Stemming the global tsunami of cardiovascular disease (Editorial). *Lancet* 2011; **377**:529–32.