

## ATHEROSCLEROSIS—THE CASE AGAINST PROTEIN—Continued

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It has previously been demonstrated<sup>17</sup> that an increased intake of heated animal protein may possibly have played an important part in the present sustained increase in the incidence of atherosclerosis. The following were the main reasons. (1) In various epidemiological surveys<sup>17, 55, 77</sup> it has been repeatedly shown that there exists a *consistently better* correlation between the consumption of animal protein and the atherosclerosis mortality than between the latter and fat intake generally. (2) Since it was now recognized that this disease process was dietary in origin, and since we were not investigating a new disease, but rather an increased incidence of that disease, search had therefore to be made for a food or a group of foods, (*a*) which was common to all the countries involved and (*b*), which had been consumed in significantly increased amounts, especially in those countries incurring a high incidence. It was found that all the countries which had in fact incurred this relatively high mortality, had also increased (mainly by virtue of pasteurization and/or of processing) their intake of heated animal protein to a significant degree. (3) That heated animal protein might be at fault, also seemed more probable when it was revealed that the Eskimo, domiciled in the uncivilized areas of the far North—mainly because of the absence of fuel—was in the habit of consuming vast quantities of raw meat and developed comparatively little evidence of the disease, whilst the Eskimo, who cooked his meat in the more civilized areas of Hudson Bay, developed a relatively high incidence of atherosclerosis.<sup>78</sup> (4) Moreover those countries, which suffered the greater incidence of atherosclerosis, namely the U.S.A., Canada, Finland, New Zealand, Australia and the United Kingdom, were shown to consume greater quantities of those meats which contained a relatively high content of cyanocobalamin,<sup>17</sup> a finding which correlated well with the original observation in this investigation, namely that cyanocobalamin, given as a tonic to atherosclerotic patients, appeared to cause a marked deterioration in their cardiovascular disease.<sup>19</sup>

(5) In the case of the Scandinavian and of the Continental countries, their high consumption of marine oils, in some cases, their

essentially rural character with a correspondingly lowered intake of pasteurized milk and milk products, their high consumption of cream rather than milk and, finally, their preference for (a) wine rather than milk and (b) for yoghurt, which has been shown to have a very low content of cyanocobalamin,<sup>27</sup> (the bacteria concerned in the fermentation of the milk seem to take up most if not all of the available vitamin may all be some of the factors tending to lower their mortality.

Moreover, such a hypothesis would seem to explain, in part at least, both the increased incidence of atherosclerosis in peptic ulcer patients<sup>7</sup> and the fact that atherosclerosis can and does occur in all age groups.<sup>22</sup>

Thus encouraged by the fact that this hypothesis appears to correlate with some, if not all, of the various conditions, it was decided to investigate the history of the mortality of this disease process and, at the same time, the history of all contemporary, available, and relevant dietary changes in order to see whether, in fact, this suggested cap does fit.

### Method

It has often been stated that the death certificate was of little or no value as a yardstick, being subject to changes of "fashion", changes due to more accurate diagnosis, and to changes in treatment, and so on. However, it did seem possible that the mortality of the age groups, known to be the most sensitive to the disease process under review, might reasonably be expected to demonstrate changes in trend, so sustained and of such a magnitude as to be obviously significant. Moreover, as it was not necessary, nor for that matter possible, to measure the exact amount of any sustained increase or decrease in incidence but rather the date of commencement and the general pattern of any such change, it was decided to extract wherever possible and record as a whole, the mortality ascribed to the following disease processes: angina pectoris, cerebral embolism and thrombosis, and embolism and thrombosis (not cerebral) (International List Numbers 89, 74c and 92 respectively), thereby revealing the changing trends of what might be termed, "generalized atherosclerosis" (GAS). The age groups chosen as the most sensitive to the disease process were those aged 55—70, both male and female. These were in turn compared with the age groups least sensitive to the disease process, both male and female aged 30—54 and with the crude mortality, which was found in some instances to conceal such changes almost completely. The Standardized Death Rates of the Registrar General also served to confirm that a significant increase or decrease had in fact occurred but, being the death rate of a population of a standard age and not of the true

population, did not demonstrate clearly when those changes actually began or, for that matter, their total extent, but only their comparative extent. Moreover, as it was known that a decreased incidence of this disease process occurred in rural areas, wherever possible the urban and rural mortality of the above mentioned age groups were also compared. Finally, all death rates were delineated in close proximity to (1) the index of the working class cost of living, shown in reverse,<sup>76</sup> or the quotient of income and wages over prices<sup>2</sup>—both these indices acting as a rough measure of the purchasing power of the nation—(2) with the estimated consumption of animal protein (G. per person per day) and (3) with that of saturated fatty acids<sup>16</sup> (G. per person per day), both the latter being estimated from the works of Prest<sup>4</sup> and Stone.<sup>9</sup> It is stressed that these food estimates are in fact *only estimates*, based mainly on export and import figures and those of different producers or manufacturers; they serve, however, to show the trend of food consumption. Complete estimates of fat consumption for the period 1900—19 were not available nor were those pertaining to animal protein derived from poultry and game for this same period. It should also be noted (figure 10) there is a difference of 2G. between the estimates of animal protein supplied by the Ministry of Food for the period 1935—58 and those supplied by Stone<sup>9</sup> for the years 1920—38.

### Early Years

During the period 1861—1900, (figure 1) there occurred an increase in the mortality ascribed to angina pectoris—in fact, according to the standardized mortality of the Registrar General, it very nearly doubled itself; if then we examine the mortality of the sexes in their different age groups (figure 1), we find that the premenopausal female shows little or no increase, whereas the postmenopausal female and the male aged 55 and over both show highly significant increases, the male obviously surpassing the female. In fact, the different age groups and the sexes have behaved as we would expect them to, with our present knowledge of the epidemiology of this disease. It seems impossible that the different sexes and age groups could have formed the correct patterns by coincidence, especially at a time of relative ignorance of this disease process. It follows therefore, that this increase in mortality must have been, to a considerable extent, real.

### *Social class*

The increase in the relative size of the middle class occurring during the period 1881—1911 amounted to 3.4 per cent for males and 11.1 per cent for females. As the males sustained a much larger rise in mortality than the females, it seems unlikely that this compara-

tively small increase in size of the middle class, brought about mainly by the industrial revolution, could have been a major factor, although it should be remembered that, during this period, angina pectoris was a disease of the middle, rather than of the working class<sup>29</sup>.

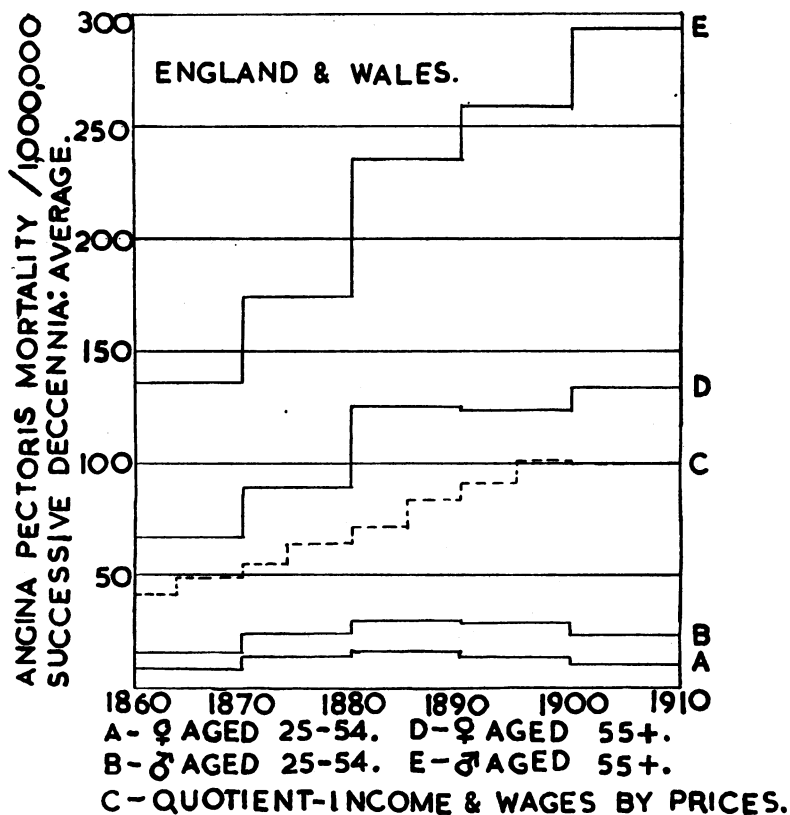


Figure 1  
Angina pectoris mortality 1860—1910

### *Ageing factor*

If we compare the standardized death rate for all ages with the non-standardized, we find that the former showed an increase in mortality of 84.62 per cent whilst the latter increased 100.9 per cent—a difference of 16.29 per cent. Thus as a rough estimate, it seems reasonable to suggest that the two factors, social class and ageing, may have been responsible for about 20 per cent of the total increase in mortality occurring during this relatively long period of fifty years.

*Dietary changes*

It is obvious from figure 1 that the maximum increases in mortality which occurred during this period, took place in the earlier decennia, 1860—1880, and, for an explanation, it would seem reasonable to investigate all dietary changes which may have occurred at this time.

In 1844, custard powder, mainly in the form of Bird's Custard, came on the British market for the first time; in America in 1856, a patent for the manufacture of sweetened condensed milk was granted and in 1866, the Anglo-Swiss Condensed Milk Company began successful operations in Switzerland. It seems likely therefore that, although condensed milk was not listed separately as a major import until 1888 (352,332 cwts in that year), importation of this popular but relatively expensive milk product commenced in the late sixties and early seventies, malt-based milk drinks such as "Horlicks" did not come on the market (American) till 1887.

Such minor dietary changes could not, of course, have been the main cause of this increase in mortality but may have played some part, as it seems likely that the middle class were the largest consumer of these "luxuries" during this period when the working class wage was relatively low and prices generally were falling—a situation, which would seem to favour especially the purse of the middle class housewife. So also may she have been more able to take advantage of the increasing imports of rice, sago, tapioca, and arrow-root, which began to flood the market from about 1840 onwards; the "milk pudding" had arrived. If then we lump together and compare such imports for the year 1860 and for the year 1877 (years in which both the necessary import and the population figures were available), we find that the increase of our imports of foods of animal origin, such as beef, pork, eggs, fish, etc., together with those of foods which were normally cooked in milk, e.g. the above listed cereals, rice, sago, coffee and cocoa, amounted to as much as 120 per cent. It should be noted also (a) that these figures did not include custard powder and condensed milk, as import figures for these items were not available, and (b) that our imports of lard and butter also increased by about 45.8 per cent in this period.

Thus the evidence of the imports of this time seems to indicate a marked increase in the consumption of heated animal protein, mainly in the form of heated milk, and, to a lesser extent, of animal fat.

**1880—1899**

In the *Statistical Tables of the Accounts and Papers* (1899)<sup>15</sup> there is related, for the United Kingdom, the estimated consumption of various foods during the period 1884—98. From these it is evident that the consumption of animal protein began to increase in 1888/89

and continued to do so until 1898 and thereafter remained at the same level—a sustained rise of about 93 per cent. These foods included beef, mutton, pork, preserved meat, eggs, and cheese. This increase was aided by the importation, for the first time in 1888, of refrigerated meat from New Zealand. Figures for fish, milk, and milk products were not available but visible fats in the form of butter and margarine\* (first listed as an import in 1886—1870, 409 cwt) also increased from 7.25 lb per person per year in 1886 to 11.25 lb per person per year in 1898 (+ 55 per cent). Coffee decreased from 0.90 to 0.69 (—23.3 per cent); cocoa on the other hand, increased from 0.39 to 0.80 lb per person per year (+ 105 per cent). No figures were available for sago, tapioca and arrowroot, but rice seemed to wane in popularity and fell from 9.85 to 7.55 lb per person per year (—31 per cent). From these figures, it would seem reasonable to conclude that, although there may have been some waning in the consumption of milk puddings, etc., the increase of 93 per cent of the various meats must have resulted in a real increase in the consumption of heated animal protein.

#### 1900—1910

During this period, the country's economy became more stable, and our quotient of income and wages over prices remained level<sup>2</sup>. The mortality from angina pectoris obediently followed suit, together with the country's consumption of animal protein and of visible fats in the form of butter, margarine, lard, and cream (figures for dripping and edible vegetable oils were not available). Animal protein, less that portion derived from poultry and game, averaged 38.41 G. per person per day and available visible fat 33.27 G. The consumption of the cereals, sago, tapioca, and arrowroot (separate figures for rice were not available) averaged 18.26 cwt per million and also did not vary significantly. Coffee and condensed milk showed no appreciable change, whilst the major part of the increase ascribed to cocoa—from 33 to 40 cwt per million—seems to have been utilised as chocolate. No significant dietary change seems to result in no change in the mortality.

#### 1910—1919

It now became possible to compare the "generalized atherosclerosis" rate of the different age groups and sexes of the urban and rural populations—GAS—the sum of the deaths ascribed to angina pectoris, cerebral embolism and thrombosis, and embolism and thrombosis (non-cerebral) per million population.

In the first instance, if we compare the GAS mortality for persons aged 55 and over in (a) London Administrative County and (b) the rural districts of England and Wales for the period 1911—14

(figure 2) we find that both the city and the rural mortality rose slowly, the former developing a peak in 1915, having risen somewhat more steeply than the latter. From 1911 both income and wages also began to rise but, as prices followed suit, purchasing power appeared to remain stable. However, in this period of relative prosperity, income and wages may have risen rather more quickly than prices and, as a result, the middle class especially, who were still the main class to be affected by atherosclerosis and who, of course, enjoyed a more favourable economy than the working class, may have been induced to spend somewhat more freely<sup>2</sup>. This assumption receives some confirmation from the fact that, as from 1911, the consumption of condensed milk began to increase and continued to do so, rising to as much as ten per cent of the total liquid milk consumption in 1919, although the consumption of animal protein in general and presumably also of saturated fatty acids, showed no significant change from 1910 to 1914. However,

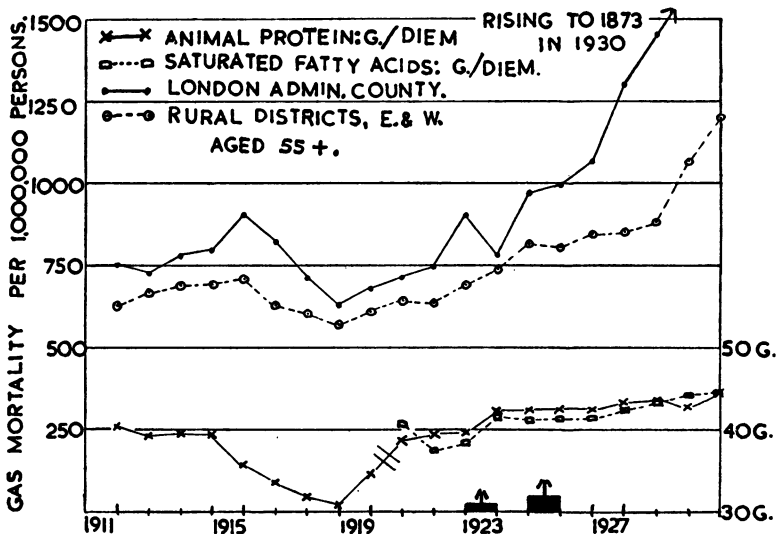


Figure 2. Death rate from generalized atherosclerosis, London Administrative County, and rural districts of England and Wales 1911—1930.

in 1915, the consumption of animal protein began to fall and continued to do so steadily until 1918. After an interval, which varied from only one to two years, the GAS mortality in most age groups (figures 2, 3, 4 and 5) also began a downward trend—except the rural females aged 35—54 and who showed no evidence of any change (figures 2, 3, 4 and 5) also began a downward trend—except the rural females aged 30—75, who showed no evidence of any change

at all in mortality. On the other hand, the fall experienced by the city age groups was obvious, increased with age and, at the same time, was, as would be expected, more extensive and more sustained in the male than in the female. Once more the age groups have behaved in the manner expected of them. Moreover, the fact that the greatest fall occurred in the older age groups of both males and females in the city, where, not only the wartime dietary restrictions (being less likely to be relieved by local produce), but also the stress of the war itself, would have been more severely felt, militates strongly against the latter as a primary factor in the etiology of this disease and would seem to favour dietary changes in this role.

### *Margarine*

In 1910, it became possible to manufacture a more popular form of margarine by using hydrogenated vegetable oils; hitherto, because it was generally insipid and unpalatable and, incidentally, cheap compared to butter, margarine had been consumed mainly by the poor<sup>1</sup>. Now, its popularity increased rapidly during the war and its consumption rose from 45.42 cwt per 1000 per year in 1910 to 148.55 in 1919.

Thus it seems possible (*a*) that the increased consumption of condensed milk during this period (1910—1919) may have helped to diminish the total extent of the fall in the consumption of heated animal protein and (*b*) that the increased intake of margarine may have lowered the general fall in the consumption of saturated fatty acids at this time.

### **1920—1930**

It should first be noted that, during this period, owing to the rapid growth of the cities, the rural districts of England and Wales, as defined by the Registrar General, were no longer truly rural, and, in fact, contained a large part of Greater London as well as the suburbs of other spreading cities and large towns.

It will be seen, however (figures 2, 3 and 4), that after an interval of one or two years—the same interval as occurred after a dietary change in 1915—following a rise in the consumption of both animal protein and of saturated fatty acids (approximately 2 G. only) in 1922, the GAS mortality of both the urban and rural populations rose simultaneously, above their highest pre-war levels; thereafter, the rural or rather semi-rural, graph continued to rise slowly parallel with the food graphs, whilst the London mortality suddenly rose precipitously in 1926—27, and the semi-rural rose more slowly three years later in 1929.

At this stage, it should be noted that up to 1926, in England and



Wales, all cases of “coronary thrombosis” had been classified with “arteriosclerosis”, and, in 1927,<sup>86</sup> a change in coding came into operation, reclassifying all cases of “coronary thrombosis” with “angina pectoris”. This change in coding was fortunate in some ways, because it has served to emphasize the essentially *urban nature* of this precipitous increase occurring at this time, because, although the urban graph rose obviously more steeply in 1927 than in 1926—an increase which must have been enhanced, at least in part, by this change in classification (the total increase in 1927 for the whole of England and Wales was as much as 33 per cent—from 1,880 in 1926 to 2,802 in 1927)—the rural graph, on the other hand, maintained its steady slow, upward trend. It follows, therefore, that the total number of cases of coronary thrombosis registered in the rural districts of England and Wales in 1927, must have been relatively small.

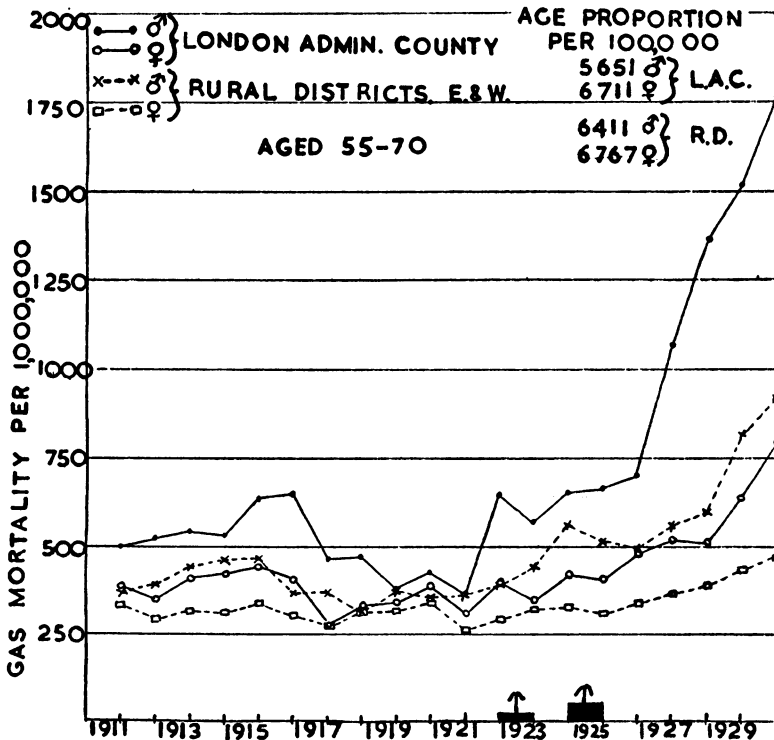


Figure 3.

Death from generalized atherosclerosis London and rural districts England and Wales, age group 55—70.

Moreover, it is obvious that, if it had been possible to extract the deaths ascribed to coronary thrombosis for each year prior to 1927, this sudden increase in mortality would probably have occurred at least two or three years sooner than it did—an increase (1) which had gone against all previous trends in that it occurred at a time when the country's economy was relatively stable—the purchasing power was actually falling slightly—(2) which had clearly and significantly singled out the urban population and not the rural—(3) which appeared to affect for the first time social classes III, IV and V, as well as classes I and II; in fact, the percentage increase in male mortality, assigned to heart diseases other than valvular,

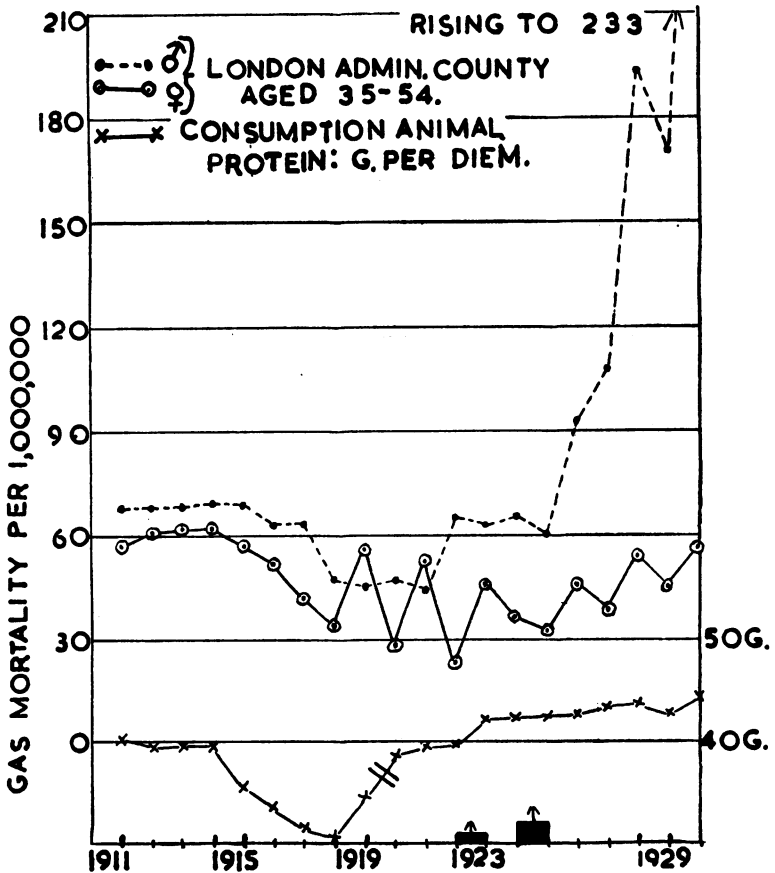


Figure 4.

Deaths from generalized atherosclerosis London Administrative County for males and females, and consumption of animal protein in grammes.

between the years 1921—23 and 1930—32 was greater in the former group of classes than in the latter; thus for males aged 55—65, the percentage increases for each class in numerical order were 63, 59, 71, 85, and 64 and for males aged 65—70, they were 60, 58, 83, 96 and 97—and, finally, (4) which once more affected the various age and sex groups of the two different aggregations in the expected correct proportions (figures 3, 4 and 5).

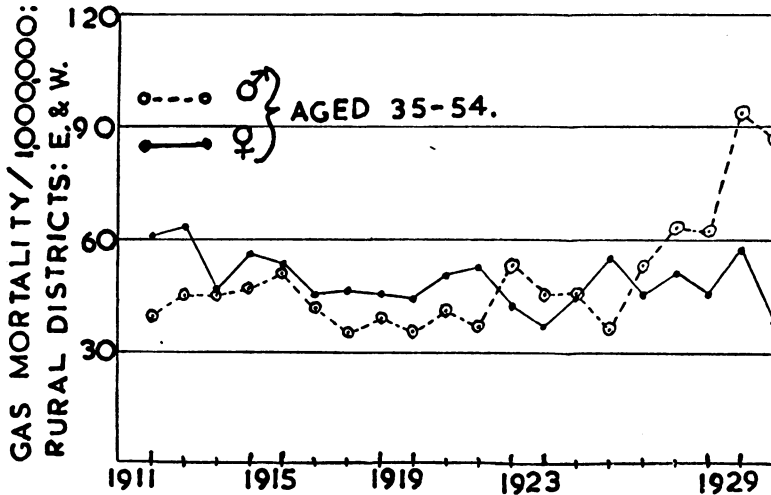


Figure 5.

Deaths from generalized atherosclerosis in rural districts of England and Wales in age groups 35—54.

Thus, if we compare the male and female age groups, aged 30—54, for (a) London Administrative County and (b) the rural districts of England and Wales (figures 4 and 5) we again see how obviously and severely the urban male population was affected, leaving the semi-rural male showing only a relatively slight rise in 1927—30 and the female age groups in both aggregations completely untouched, thus demonstrating once more that the different sexes and age groups have behaved in the manner expected. When such a change in trend fulfills all these conditions, and, what is more, is sustained, it would seem certain that this sudden drastic increase in mortality must be, after all, for the greater part, a real increase and is obviously not the result either of a change of fashion or of diagnosis or, altogether, the result of ageing, (of which more anon) or, for that matter, of a summation of these factors. For the cause of such a sudden and precipitous rise in mortality, it would seem more reasonable to search once again for a sudden dietary change—a change which

must affect both the working class and the middle class, and the urban rather than the rural population, and which, incidentally, must affect the different sexes and their different age groups, all in the correct proportions.

As already mentioned, the graphs for the consumption of animal protein and of saturated fatty acids showed a slight rise of approximately 2 G. in 1923, a rise which coincides with the purchasing power graph, now finding its correct and more stable post-war level. One year later, the mortality in both London and the rural districts obediently followed suit. For the sudden rise commencing in 1926—27 in the city, on the other hand, there is no obvious dietary change to account for it, at least in the food graphs shown, and, although part of the rise in 1927 is explained by the change of coding already mentioned, the further drastic increases remain unaccounted for.

#### *Pasteurization*

Therefore, it must be something more than a coincidence that, as from 1 January 1923, the Milk and Dairies (Amendment) Act (1922) took effect, requiring that all milk sold as “pasteurized” must be treated by the “Holder” method, i.e. heated for 30 minutes at a temperature of not less than 145°F. and not more than 150°F., and then rapidly cooled to not more than 55°F. It seems clear also that such prolonged heat treatment would normally free a large percentage of the cyanocobalamin in the milk. Thus Ross,<sup>31</sup> after heating horse serum for 30 min. at 158°F. obtained 70  $\mu\mu\text{g./ml.}$  free cyanocobalamin, whilst the same treatment at 132°F. gave growth equivalent to 13  $\mu\mu\text{g./ml.}$  only, and at 212°F., it gave 220  $\mu\mu\text{g./ml.}$  On the other hand milk treated by the “Flash” method of pasteurization, i.e. which was heated for 16 seconds only, at 165°F. gave values of 2.5—5.3  $\mu\mu\text{g./ml.}$  only.<sup>27</sup>

Here therefore, there has occurred, once more, a significant increase in the amount of animal protein, which has received some kind of heat treatment before consumption—up to 16 per cent of the total amount in 1924—an increase which also commenced suddenly in the years immediately preceding this highly significant and sudden rise in GAS mortality, which was readily available to *all* social classes for the simple reason that pasteurized milk was the cheapest of the designated milks, and which, for obvious reasons, was consumed in far greater quantity in the urban areas than in the rural districts.

#### *“Holder” pasteurization in various cities*

An attempt was then made, first to ascertain the history of the pasteurization of milk in London and in the various cities of Scot-

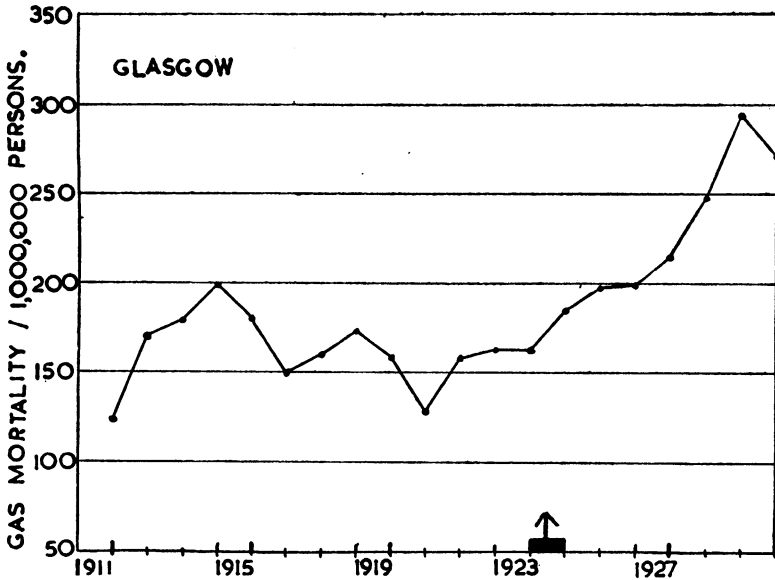


Figure 6.

Generalized atherosclerosis mortality for Glasgow, 1911—1930. (The arrow indicates when Holder pasteurization commenced.)

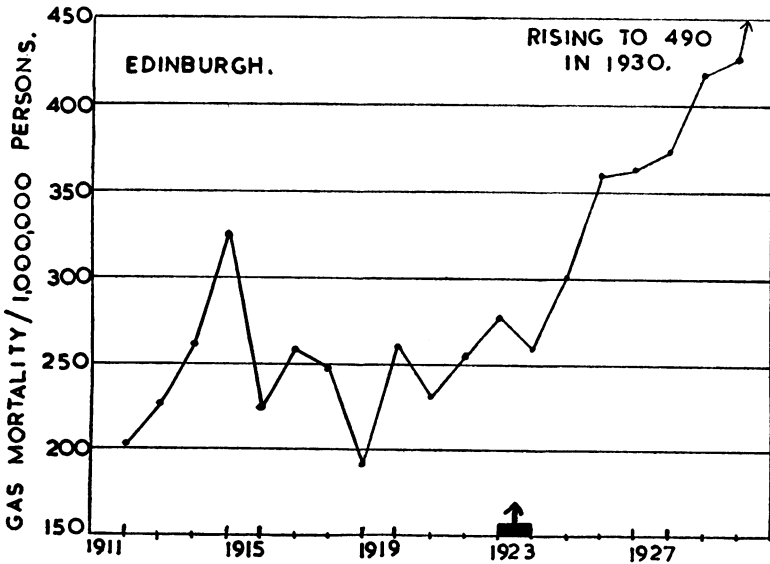


Figure 7.

Generalized atherosclerosis mortality for Edinburgh, 1911—1930. (The arrow indicates when Holder pasteurization commenced.)

land, and then to compare it with the GAS mortality graph. The results are shown in figures 2, 6, 7, 8 and 9, where the arrow indicates the year in which "Holder" pasteurization commenced in each case, and it will be seen immediately that "Holder" pasteurization preceded the sustained rise in mortality by the same interval of time as occurred after other dietary changes in trend, namely 1—2 years, in every city, except perhaps London, where the interval may have been, if anything, longer; here the evidence for the opening of the various dairies was very scanty, and only two or three small pasteurizing plants came into operation prior to 1925, when the larger creameries began to open.

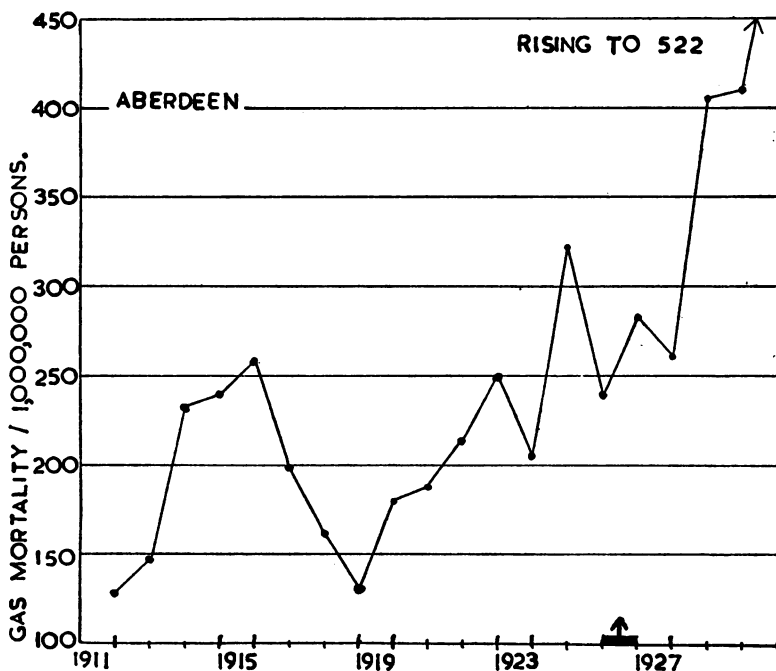


Figure 8.

Generalized atherosclerosis mortality for Aberdeen, 1911—1950. (The arrow indicates when Holder pasteurization commenced.)

It should also be noted (1) that varying types of the "Flash" method of pasteurization were in use, mainly in small quantity, in London, Glasgow, Edinburgh, and Aberdeen during the first two decades of this century. There was no evidence, however, that any significant rise in GAS mortality occurred as a result, although it may have contributed in some part at least. (2) There was *no change of coding in Scotland* such as occurred in England and Wales

in 1927. (3) Cerebral embolism, for which separate figures were available for the period 1921—30 for England and Wales, showed a steady fall, from 13.03 per million persons in 1921 to 7.17 in 1930. It seems likely therefore that the increase ascribed to cerebral thrombosis was even greater than those shown. (4) In general, it can be said that, at the time of the sustained increases, both angina pectoris and cerebral embolism and thrombosis started rising together, either during the first or during the second year of the

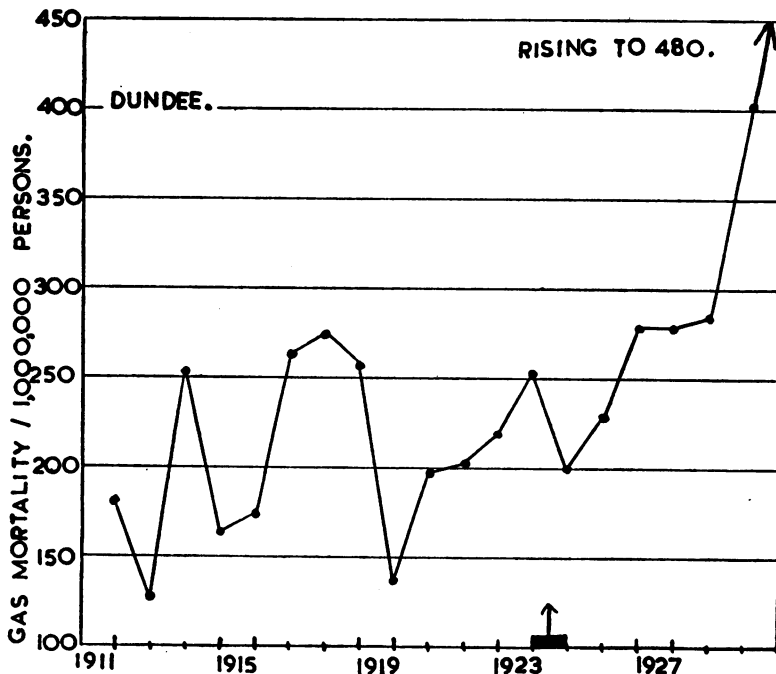


Figure 9.

Generalized atherosclerosis mortality for Dundee, 1911—1930. (The arrow indicates when Holder pasteurization commenced.)

increase. Embolism and thrombosis (non-cerebral), on the other hand, showed no consistent rise until the late twenties.

#### 1929—1938

If we turn now to figure 10, which compares the crude GAS mortality of the City of Edinburgh with that of six counties of Scotland, (Banffshire, Berwick, Kincardine, Kinross, Sutherland, and Ross and Cromarty), chosen because they contained no large towns and because they had not been supplied with pasteurized milk during the period under review, and again, with the graphs

showing the consumption of animal protein and of saturated fatty acids and finally, with the graph of purchasing power, i.e. the index of the working class cost of living, shown in reverse, we find that the crude urban mortality clearly commenced its sustained rise 1—2 years after the beginning of "Holder" pasteurization, and thereupon rose clear of the rural mortality, which, in turn, commenced a sustained increase in 1929 and then, rather surprisingly, overtook the former in 1931. Thereafter, both continued a slow steady increase till 1939.

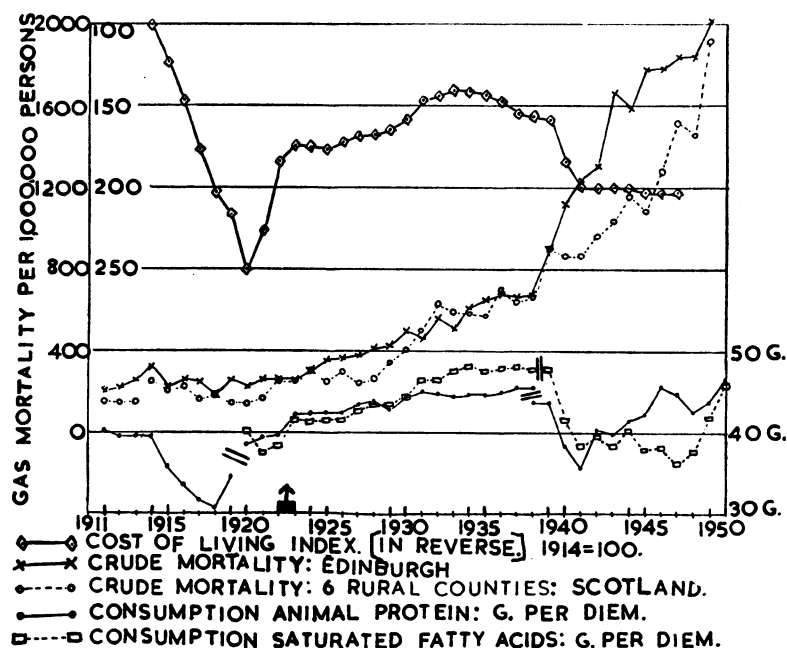


Figure 10.

The crude mortality (generalized atherosclerosis) in Edinburgh and six rural Scottish Counties.

For an explanation of these changes in mortality trend, the following points may well be relevant. (1) The 1929 rise in rural mortality coincided with a sharp rise in the purchasing power<sup>2</sup>, due mainly to a fall in prices, which occurred at the beginning of the economic depression and continued till 1933, when prices started rising once more. (2) The country van had begun to bring a more urban-like diet to the door of the country house. As a result, the country housewife had every opportunity to enlarge and vary her menu, her purchasing power being favoured rather than adversely affected by the falling prices of the economic depression, whilst the purse of the city working class, especially, was most severely



depleted. Thus again we see the urban and rural mortality graphs approximating one towards the other. (3) It will be seen also, that an increase in the consumption of saturated fatty acids began about 1930—31, an increase which was mainly due to a rise in the consumption of butter, and which, it should be noted, *followed the rise in rural mortality and was not followed by a commensurate increase in mortality*, either in the city or in the country. (4) During all this time, there had occurred a steady increase in the consumption of the following foods,—condensed milk, milk powder, ice-cream, cakes, biscuits, and tinned meats. The manufacture of cheese from pasteurized milk and the production of processed cheese were also both proceeding apace. If, then, we compare the diet of the urban citizen in 1921 with that of the same citizen in 1938, and, if we assume that one third of his milk was heated prior to consumption in 1921, and that he consumed only pasteurized milk and pasteurized and/or processed cheese in 1938, and farm cheese only in 1921, it will be found that the “average” citizen will have increased his intake of heated animal protein by as much as 45.45 per cent in 1938. (5) It would also seem reasonable to suggest that (a) the lifting of the economic depression in the city and (b) the above-mentioned accumulated increase in the consumption of heated animal protein, which, as already shown, must have occurred in both urban and rural areas, (the latter being, of course, less affected) would well account, in part at least, for the fact that both the mortality graphs in figure 10 carried on a slow increase during the period 1933—38, both going against the current dietary and economic trends.

### 1939—1958

During the thirties, (exact dates unknown) at least four large creameries began operating in Edinburgh, thus augmenting the City's supply of pasteurized milk by approximately 333,200 pints per day. From our previous findings, it is reasonable to suggest that here we may have a possible partial explanation for the sustained, precipitous rise in the urban GAS mortality, beginning in 1939—40, going almost diagonally opposite the economic and dietary graphs, and showing no sign of responding to the war-time fall in the consumption of animal protein and of saturated fatty acids, as did the rural graph. The fact that the latter did now show a partial response to the dietary changes would be a possible confirmation of our previous suggestion that the rural diet was *now* more urban in type than it had been during, for example, the 1914—1918 war, when the rural mortality failed to fall in line with diet.

By regulation in the early forties, the “Flash” method was now permitted, and, being popular, rapidly gained ground. A considerable drop in the dietary content of “free” cyanocobalamin would

thus result and may account for the fact that the city mortality graph flattened out about 1944—45 and once more approximated towards the rural graph.

It should also be noted that the consumption of saturated fatty acids did not rise again to its pre-war level until 1950.

Thereafter, under the Special Designation (Specified Areas) Order, 1951, more and more districts throughout the United Kingdom came to be supplied with milk, pasteurized either by the "Flash" or by the "Holder" method, the former predominating. Moreover, from 1952 to 1957, the consumption of animal protein in relation to vegetable protein, has shown an increase of ten per cent. Fat consumption, in general, has increased only three per cent during this time.

### The Ageing Factor

Just what part increasing age has taken in this mortality rise has long been a controversial point. However, if, in the first instance, we compare the age proportion<sup>14</sup> with the GAS mortality of the different sexes aged 55—70 in (a) the rural districts and (b) in London Administrative County, for the period 1920—30, (figure 3) we find that the groups which had the highest age proportion had the lowest mortality; thus, even the London male, the most sensitive, had a lower age proportion (— 11.8 per cent) than the rural male of the same age group. In fact, the correlation was completely reversed. Moreover, these same groups, which remained in the same age proportion throughout this period, showed trends which were the reverse of the expected as far as age was concerned. Thus the rural female, by far the oldest, showed only a comparatively slight upward trend towards the end of the period, with no fall at all during the war; the London males, on the other hand, the youngest, demonstrated a highly significant decrease during the war period and, thereafter, a precipitous rise. Moreover, when we compare the same groups, this time aged 30—54 (figures 4 and 5) we find that, while the female showed no alteration in mortality trend whatsoever, the male was dramatically picked out in both aggregations, and, of course, especially in the urban group, in spite of the fact that, according to the census figures, the London male of this group had a smaller age proportion (— 2.3 per cent) in 1931 than they had in 1921.

The failure of the crude GAS mortality in Edinburgh (figure 10) to show a more significant fall during the 1914—18 war can perhaps be explained by the fact that during this war, in Edinburgh and in most Scottish cities, there occurred an increase in the incidence of cerebral embolism and thrombosis, an increase which also occurred in

social class V at this time<sup>32</sup> and may thus be ascribed to a possible dietary deficiency.

### Social Class

It has long been known<sup>13</sup> that social class and/or sedentary employment play an important part in the epidemiology of this disease. Accordingly the urban and rural populations were compared in this respect and, from census returns, it was found that, in 1931, there were seven per cent more people in social classes I, II, and III in the urban areas than in the rural districts, and in Edinburgh, there were 5.8 per cent more employed in sedentary work than in the six rural counties listed. It is impossible to estimate just what effect such a difference in employment and/or social class would have on mortality but it does not appear likely that such a small difference would cause a major rise in mortality; however, the opposing effects of the greater age of the rural population, on the one hand, and the greater numbers of the urban middle class, on the other hand, would probably cancel each other out.

### Socio-economic Groups

Comparison of (a) the estimated consumption of animal protein and of saturated fatty acids of the various socio-economic groups<sup>80</sup> with (b) the Standardized Mortality Ratio attributed to coronary disease, angina pectoris (International Number 420) and estimated by the Registrar General<sup>81</sup> for males aged 20—64 of these same social groups, immediately reveals (figure 11) once more, a better correlation between the consumption of animal protein and the mortality than that between the intake of saturated fatty acids and the mortality. (The dividing line in each column, which is a measure of the mortality, gives the consumption of animal protein—the left hand group—and of saturated fatty acids—the right hand group). Moreover, the agricultural worker, who has the lowest mortality, and is most probably the highest consumer of fresh milk and cheese, and, therefore, is the lowest consumer of heated animal protein, *actually had a larger intake of saturated fatty acids (+ 1.93 per cent) than the professional class.*

### At the International Level

An attempt was made to obtain the necessary mortality figures for the various civilized countries and to compare them with the pasteurization programme in each. Unfortunately, for various reasons, these have not been generally available and, only in the case of Denmark, Finland, and Switzerland, has it been possible to make comparative graphs.

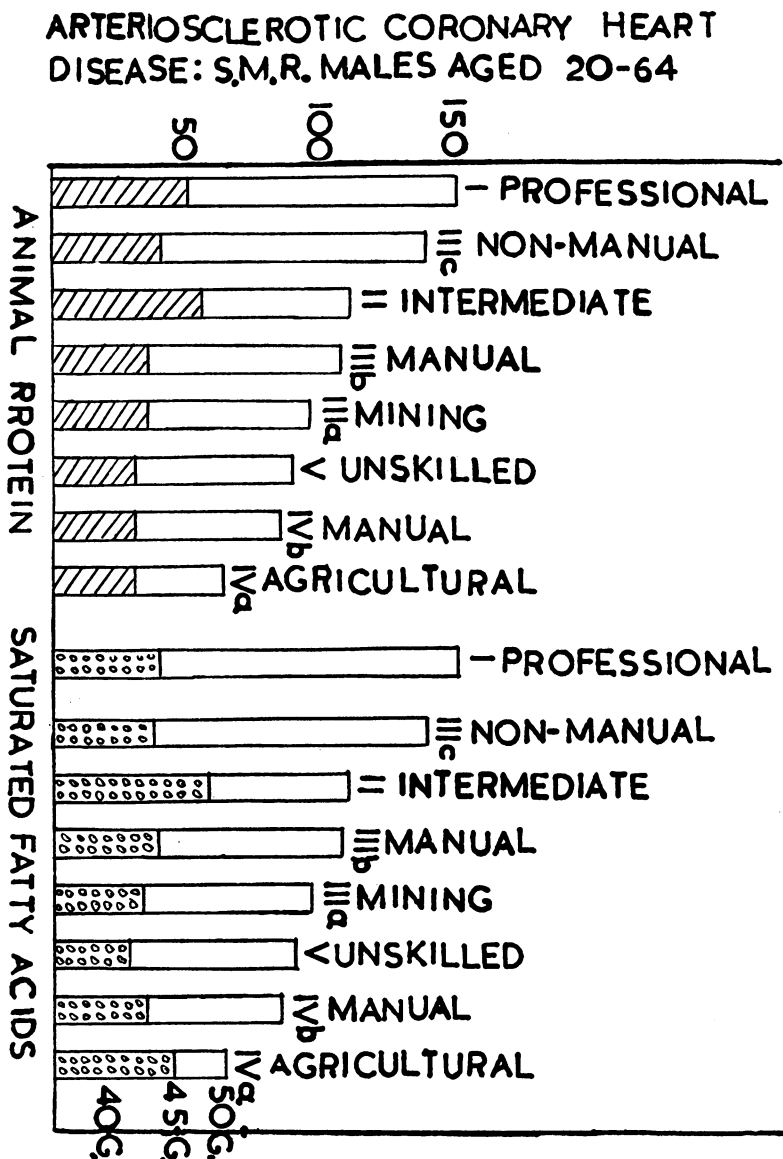


Figure 11.

Arteriosclerotic coronary heart disease mortality and animal protein and saturated fatty acid consumption by occupation.

Moreover, the mortality figures for Denmark have been affected by a change (a) in coding in 1946 and (b) in nomenclature in 1951. In the former case, in 1946, "Senilitas" was withdrawn as a primary

cause and the secondary cause substituted; as a result, it has been impossible to estimate the extent of the effect of this change in coding. However, it will be seen (figure 12), that a rise in mortality commenced in 1944, the year in which general pasteurization became compulsory in Copenhagen and in Frederiksberg and, thereafter, throughout Denmark as a whole and, this rise commenced two years before the change of coding in 1946. The type of pasteurization used was either "Flash" or "Holder"—the former mainly in the cities, and both in the rural areas.

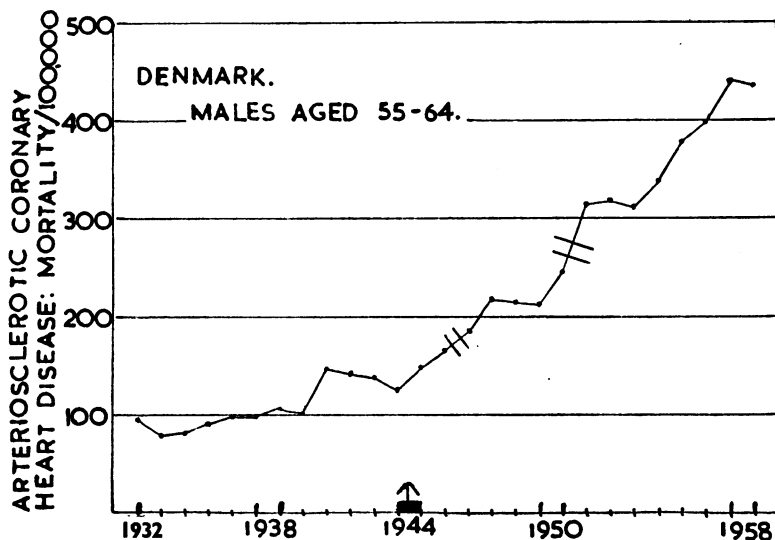


Figure 12.

Arteriosclerotic coronary heart disease mortality, Denmark, 1932—1958.  
(Pasteurization commenced 1944.)

It is unlikely that the change in nomenclature, which occurred in 1951 in all three countries, had any significant, *sustained* effect.

On the other hand, in Finland (figure 13), a sustained clearcut increase in mortality commenced immediately after the introduction of a regulation on 5 November 1946 enforcing pasteurization (mainly "Flash") throughout the country. Prior to this time, in both Denmark and Finland, pasteurization had been on a voluntary basis only and had been carried out mainly in the cities. It seems possible that this rise in mortality in Finland may have been enhanced during the years 1951—52 by the change in nomenclature (figure 13). It should be noted that crude mortality figures only were available for Finland.

Finally, in Switzerland (figure 14), where the pasteurization of

milk has not been generally carried out—only ten per cent in 1958,—no comparable increase in mortality has occurred.

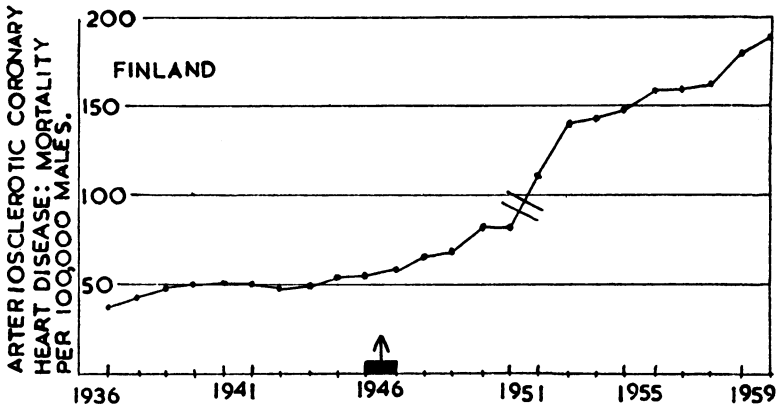


Figure 13.

Arteriosclerotic coronary heart disease mortality, Finland, 1936—1959. (Pasteurization commenced 1946.)

### Diet

During the last three years in this practice, all patients who showed evidence of atherosclerosis or who seemed likely to develop this disease, have been advised to maintain a diet low in heated animal protein and in cyanocobalamin, and high in vegetable protein and in ascorbic acid. Thus, as previously related,<sup>17, 19</sup> for the first 6—8 weeks, all fresh cases were allowed approximately one pint of unheated milk per day, and an occasional small helping of white fish or of pig meat, no cheese, beef, mutton, chicken, game, eggs, offal, and no fish of a high cyanocobalamin content, such as salmon or sea trout;<sup>17</sup> they were also advised to increase their intake of cereals, fruit, and vegetables, with the emphasis being placed upon foods which have a high content of vegetable protein, such as cereals, peas, beans, lentils, and nuts and upon foods with a high content of the "vitamin B complex", such as wholemeal bread and oatmeal; they were also given ascorbic acid 25 mg. twice or thrice per day. Thereafter, they were advised to maintain the above diet, now adding small helpings of veal, herring and an occasional egg. All milk must be consumed fresh and unheated; they were not allowed milk puddings, custards, ice-cream, milk chocolate, milk powders, tinned milk drinks, or any type of cheese.

### Results

During the year February 1960—February 1961, all cases in this practice and, as a control, all cases in a neighbouring practice show-

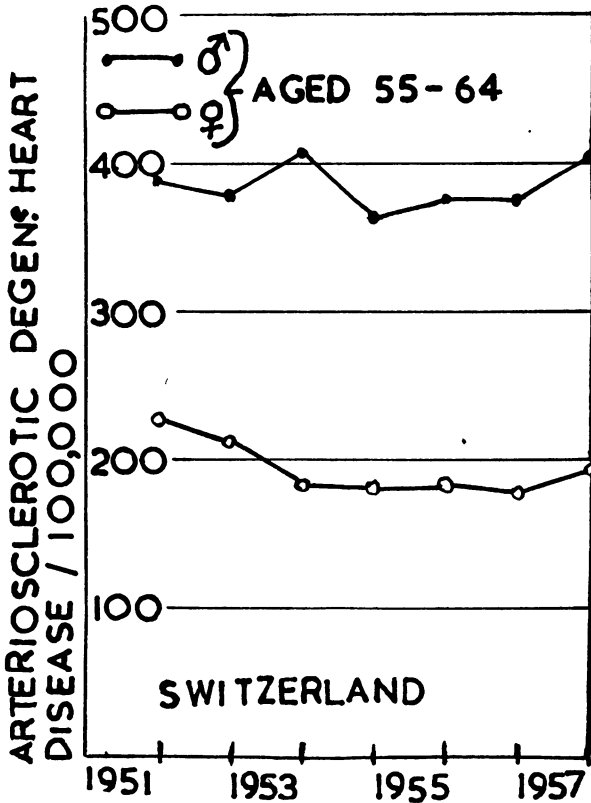


Figure 14.

Arteriosclerotic degenerative heart disease mortality in Switzerland where no routine pasteurization is carried out.

ing clear cut evidence of atherosclerosis—excluding in both practices all those treated with anti-coagulants—have been carefully listed and their progress noted (table I).

**Other Factors**

It is emphasized once more that it is essential to maintain the patient's "general condition". Thyroxin and oestrogen are, of course, paramount here, but so also are the vitamins; in this respect, attention is directed to the findings of Pemberton and Thomson,<sup>87</sup> who reported an almost universal shortage of calcium, vitamin A, B and C, occurring in practically all social groups in this country during the thirties. Moreover, comparison of the present national diet with the diet of this pre-war period, cannot lead to complacency in this respect. Thus, although there has been an improvement in

TABLE I  
THE EFFECT OF RESTRICTING HEATED ANIMAL PROTEIN AND CYANOCOBALAMIN  
ON MORBIDITY FROM CORONARY ATHEROSCLEROSIS IN WRITER'S PRACTICE.

	<i>Dieted practice</i> (2,545)		<i>Control practice</i> (6,623)	
	<i>No. of cases</i>	<i>Percentage</i>	<i>No. of cases</i>	<i>Percentage</i>
1. Total incidence ..	44	1·73	113	1·71
2. Remaining stationary ..	8	18·2	44	39
3. Improved .. ..	35	79·6	28	24·8
4. Improving on diet, re- lapsing whilst off diet and again improving on diet .. .. .	23	52·3	—	—
5. Not dieted and deteri- orating .. .. .	1	2·3	41	36·3
6. Died whilst maintaining diet .. .. .	1	2·3	—	—
7. Died while not on diet	4	9·1	17	15·1
8. Incurring coronary thrombosis, as con- firmed by electrocardio- gram, whilst not on diet	1	2·3	14	12·4
9. Incurring coronary thrombosis, as con- firmed by electrocardio- gram whilst on diet ..	—	—	—	—

1. The total incidence has not altered significantly and is slightly higher in the dieted practice.

2. Considerably fewer in the dieted practice failed to improve.

3. The total number showing improvement in the dieted practice is obviously larger than in the control practice.

4. A high percentage failed to maintain the diet, mainly because of lack of support either by the press or by television or by their friends. After relapsing, they improved once more after they resumed the diet.

5. One case failed to diet altogether and went steadily downhill, dying after his fourth thrombosis.

6. One case, suffering from severe angina pectoris and myxoedema, did not tolerate thyroxin; he died, apparently suffocated whilst vomiting, after a severe attack of either angina pectoris or of coronary thrombosis.

7. This group either failed to maintain, or, as in the case of the control practice, were not instructed to maintain, their diet. Autopsy was not permitted in any of the cases who died.

8. One case in the dieted practice, shown by electrocardiogram to have developed coronary thrombosis, was found to have been off diet for a period of three months prior to the final incident.

9. It seems highly significant that none of the patients who maintained their diet developed coronary thrombosis, as confirmed by electrocardiogram.

The impression has thus been formed that, whilst there has been no decrease in the incidence of atheroma, there has occurred a marked fall in the incidence of thrombosis (81·7 per cent), a reversion in fact to the period 1908—13, already mentioned and previously described by Morris.<sup>56</sup>



most of these dietary factors, it should be noted that the nation's intake of ascorbic acid has been falling during the last few years, and that the occurrence of (*a*) dry, scaly, hyperkeratotic skin, and of (*b*) a patchy glossitis of the tongue, with or without cheilosis, are by no means rare, either in children or in adults.

Judicious "slimming" where required, and/or the exhibition of sedatives, and/or the careful control of daily exercise are, of course, all of considerable value.

### Discussion

In this attempt to interpret the atherosclerosis mortality and compare it with the socio-economic and dietary trends, it seemed clear that whenever and wherever a significant increase or decrease in the consumption of heated animal protein occurred, so also rose or fell the mortality from atherosclerosis. That the same could be said for fat was also obvious in the early years, especially in the early twenties, when the graphs for both animal protein and saturated fatty acids followed each other closely. However, if we examine once more the period 1860—80,<sup>3</sup> it is clear that, whilst there may have occurred a small increase in the animal protein and fat consumption, there was no real evidence of a major rise in the consumption of these food-stuffs; there was, however, ample evidence of a large increase in the consumption of heated milk,<sup>15</sup> mainly due to the introduction of custard powder, of condensed milk, of coffee and cocoa, and of the cereals such as rice and sago. It seems reasonable to conclude that, although the total consumption of animal protein may not have increased in any great amount, there did occur a significant increase in the consumption of heated animal protein, contemporary with a marked rise in the mortality.

Thereafter, from 1880—1900, any waning in the popularity of the milk pudding seems to have been out-weighted by a major increase in our imports of frozen meats, etc., an increase, which seems to have been taken up mainly by the working classes,<sup>3</sup> who were at last beginning to enjoy an improved economy.

As already related, no change in the food intake during the period 1901—10, seems to have resulted in no change in mortality.

On the other hand, from 1910—14, there has occurred in all the older age groups, except the rural female and in none of the younger groups—in other words, in the most sensitive groups—a slight rise in the GAS mortality—a rise which was contemporary with two dietary changes, an increased consumption of condensed milk and of margarine. The latter, being relatively cheap, was consumed mainly by the working class, whereas the former, being expensive, was a food of the middle class—who were still at this time the society

group most affected by atherosclerosis. Again, heated animal protein appears to loom large in the diet of the most sensitive age groups of the correct social class at the correct time—a finding which receives further support from the fact that there has been no evidence forthcoming to show that fat, cooked or heated to normal pasteurization temperatures, was in any way more harmful<sup>52</sup> or more atherogenic<sup>53</sup> than unheated fat.

When we consider the response which occurred (1) as related in this practice, (2) during the 1914—18 war, (figures 2 and 3) and again in the early years of the 1939—45 war,<sup>17, 55</sup> there seems to be no doubt that this disease process reacts quickly—within 1—2 years—to dietary change—a fact which becomes especially significant when we find that no sudden change in mortality occurred subsequent to the 1929—31 increase in the consumption of saturated fatty acids (figure 10), or in keeping with the prolonged fall in the dietary content of saturated fatty acids during the years 1939—49.

Finally, the complete failure of the saturated fatty acids in the diet of the various socio-economic groups to correlate with the mortality, militates once more most strongly against the hypothesis that saturated fatty acids have a *primary* role in the etiology of this disease.

#### Mode of Action

Therefore, by force not only of accumulated evidence but also of elimination, the hypothesis that heated animal protein may be one of the primary factors in the etiology of this disease, deserves most careful examination—a conclusion, which also receives further support from the well known finding that, of the three foods, carbohydrate, fat, and animal protein, the latter alone has been found capable of causing a significant rise in the metabolic rate—as high as 35 per cent in some instances<sup>58</sup>—a finding which correlates well with the fact that cyanocobalamin has also been found capable of raising the body temperature<sup>34</sup>. That this action on the metabolic rate may well be highly dangerous becomes obvious on consideration of the following points. (1) Thyroxin not only enhances the delayed type of tissue reaction<sup>83</sup> but also experimental atherosclerosis *per se*.<sup>84</sup> (2) Cyanocobalamin lowers the blood level of ascorbic acid,<sup>34</sup> which, in turn, is intimately concerned with collagen formation.<sup>60</sup> (3) Willis and Fishman<sup>59</sup> have already described a patchy deficiency of ascorbic acid occurring mainly in the areas of stress in the human arterial tree, precisely where the atheromatous plaque tends to occur.<sup>82</sup> (4) Both cyanocobalamin<sup>18</sup> and animal protein<sup>35</sup> have already been found capable of increasing the permeability of the cell membrane.

It is possible too that an explanation for this action on membrane

permeability may also be found in the metabolism of the -SH group. Thus cyanocobalamin not only spares methionine but also maintains glutathione in the reduced state,<sup>36, 46</sup> which in turn reduces dehydro-ascorbic acid<sup>37</sup>—an important factor in the desensitization brought about by the glucocorticoids,<sup>48, 71</sup>—which are in their turn, blocked in their action by all three, i.e., by methionine,<sup>48</sup> by reduced glutathione,<sup>39, 38</sup> and by cyanocobalamin itself<sup>40, 47, 49</sup>.

This suggested *modus operandi* has been further complicated by the findings of Lovei *et alia*,<sup>44</sup> who have suggested a possible central action for the specific dynamic action of animal protein, as they obtained a poor response to protein in patients suffering from Addison's disease, Simmond's disease and from diabetes insipidus. Whether the vitamin has a central or a peripheral action, or perhaps a modicum of both, the evidence all seems to point to an interference with the action of the glucocorticoids and a resultant permissive action as regards aldosterone—a situation, which becomes even more fraught with danger when we learn that cyanocobalamin has been found to increase significantly the prothrombin content of the blood.<sup>33</sup>

Moreover, although the fact that cyanocobalamin possesses a lipotropic action<sup>36</sup>—demonstrable in animals,<sup>61, 66</sup> occasionally in the young adult,<sup>41, 65</sup> but apparently not in the elder<sup>43</sup>—would appear at first sight to weigh against this vitamin being an important factor in the etiology of atherosclerosis, it immediately falls into line, when we consider the findings of Morris,<sup>56</sup> namely that, on comparing the post-mortem reports of the period 1908—13 with those of 1954—56, coronary atheroma *per se* has become rarer in all age groups, whereas the thrombosis rate is now more than double.

It should also be noted that cyanocobalamin has been found to increase the amount of free cholesterol in the blood of rabbits<sup>61</sup> and, although such a change appears to be doubtful in the human atherosclerotic,<sup>50, 51</sup> free cholesterol does appear to occur in increased amounts in the human lesion itself.<sup>45</sup> In this connection, although there seems to be no doubt that cyanocobalamin is concerned with both cholesterol and phospholipid metabolism,<sup>62, 63</sup> the vitamin's connection with the triglycerides, which also seem to be involved in atherosclerosis,<sup>51, 54</sup> awaits elucidation; however, cyanocobalamin's close link with methionine and choline, and in turn, the latter's control of lipid metabolism in general, via the liver, as suggested by Olson,<sup>64</sup> seem to provide a reasonable explanation.

*Intermediate metabolism.* The recent findings of Schrade, Boehle and Biegler<sup>51</sup> are of considerable interest, namely that, in the human atherosclerotic, whilst the ketone bodies were markedly

decreased, the blood pyruvic acid and lactic acid were both significantly increased; the effect of prolonged administration of excess animal protein and/or of cyanocobalamin in this field does not appear to be known, but there seems to be no doubt that this vitamin is vitally concerned with all three metabolites,<sup>36</sup> and, if administered in excess, can cause hyperglycemia.<sup>67</sup>

*Pernicious anaemia.* The evidence that pernicious anaemia may not be, after all, a simple deficiency disease is slowly mounting. Thus Ungley,<sup>68</sup> as long ago as 1952, drew attention to the severe toxic manifestations which frequently occurred in patients so afflicted, and especially pointed out the interesting fact, amply confirmed, that the serum from patients in relapse inhibits the maturation of the megablasts in marrow culture, and inhibition which can be overcome by adding sufficient folic acid, citrivorum factor, normal serum or cyanocobalamin in gastric juice. More recently, Schwartz<sup>69</sup> has shown that, in some cases, pernicious anaemia may be an auto-immune disease, as he was able to demonstrate the presence of antibody to intrinsic factor in the serum of 36 out of 91 patients. On the other hand, Heathcote and Mooney<sup>70</sup> have produced evidence that, in some instances, pernicious anaemia may be caused by a failure of gastric proteolysis, as they found that an oral cyanocobalamin-peptide complex produced better results than the crystalline vitamin *per se*.

### Miscellaneous

(1) It has now been shown, in controlled trials, that the reduction of serum lipids, whether by the exhibition of oestrogens or by a low fat diet, does not reduce the mortality.<sup>85</sup>

(2) Even cigarette smoking, a well known etiological factor, has been found to alter the taste of the addict, so that he increases his intake of animal protein.<sup>75</sup>

(3) Finally, it seems that the necessity for a diet high in so-called "first class" animal protein is no longer accepted,<sup>74, 79</sup>. This becomes evident when we remember that our ancestors of only 100 years ago did not suffer from Kwashiorkor and neither, for that matter, does the greater part of the present world population. That something is far wrong with our present diet also becomes obvious when we find that, unlike, for example, that of the cereal consuming Bantu,<sup>73</sup> it does not sustain lactation.

### Summary

A chronological study of the history of atherosclerosis in the United Kingdom from 1860 onwards reveals a close correlation between the intake of heated animal protein and mortality. A similar correlation is also demonstrated in Denmark, Finland and

Switzerland and, finally, in the various socio-economic groups of the Registrar-General, England and Wales.

A diet, low in cyanocobalamin and in heated animal protein, and high in ascorbic acid and in vegetable protein, was found to be effective as a prophylactic against coronary thrombosis, but not apparently against atheroma.

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