The nature of the coronary problem

The Strickland Goodall Memorial Lecture

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Master, Wardens, Members of the Court of Assistance, Ladies and Gentlemen, I was honoured by your invitation to deliver this triennial lecture in memory of Joseph Strickland Goodall, one of the first physiologists who turned to clinical cardiology, and cardiology owes much to those who have applied physiological techniques to problems of diagnosis and treatment. Coronary disease has not yet been chosen as a subject in these lectures, and it illustrates that we have now reached a turning point in attempts to reduce the mortality from heart disease for, if we are to progress in this field, we must, to some extent, divert our attention from diagnosis and treatment to epidemiology and prevention. Dr. Strickland Goodall would, I believe, have approved this approach, for in his later years his mind turned in this direction; in 1928 he wrote under the title 'The Growth of Heart Disease in This and Other Countries', and expressed the opinion that heart disease was not only increasing but also occurring at an earlier age, especially in the form of sudden death.

One view of the nature of the coronary problem has been recently, and ominously, expressed by the Council of the World Health Organization (1969):

'Ischaemic heart disease, or coronary heart disease, has reached enormous proportions, striking more and more at younger subjects. It will result in coming years in the greatest epidemic mankind has faced unless we are able to reverse the trend by concentrated research into its cause and prevention.'

Size of the problem

Without doubt the most important single facet of the coronary problem is its size, but it is not easy to assess accurately the present mortality from this disease. This is quite another problem from the controversy, which has gained some momentum in recent years,

concerning the reality of the apparent rapid increase in coronary mortality in the past forty years. Mortality statistics based on death certification may have some validity since the International Classification of Diseases was revised in 1948, but conclusions drawn from them can be only tentative. On the basis of recent World Health Organization figures for the six countries with the highest male mortality (U.S.A., Canada, England and Wales, Scotland, Australia, and Denmark), Oliver (1969) has pointed out that, between the ages of 45 and 54 years, one-third of male deaths are due to this disease, and even in the 35-to-44 age-group, one-quarter of all male deaths arose from this cause.

In England and Wales an analysis of male deaths in insured persons between 30 and 60 years of age gives closely corresponding figures; 37 per cent of adult male deaths were certified as due to coronary heart disease (Table 1).

Population studies may provide a more accurate indication of the causes of death, but they are open to the objection that the group is not representative, and they are usually undertaken in populations with a high coronary mortality. A Mayo Clinic study of the Rochester population, in which there is a 73 per cent necropsy rate, showed that coronary heart disease was the cause of death in 4 of 10 men, and 2 of 10 women (Spiekerman and his colleagues, 1962). Population studies are particularly valuable for the information they give about morbidity as well as mortality. Several groups of investigators (Kannel, Barry, and Dawber, 1963; Pell and D'Alonzo, 1964; Chapman and Massey, 1964; Doyle, 1966) have shown that in men aged 40 who are free from clinical coronary disease clinical manifestations of coronary disease (other than angina or a positive effort test) will appear each year in about 1 per cent, so that by age 65 one-quarter have developed overt coronary disease.

It would be wearisome to quote more ex-

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TABLE 1 747 consecutive male deaths, age 30-59, in insured persons, England and Wales 1967-68

Age-group	All deaths	Coronary	Deaths per cent
30-39	73	15	21
40-49	215	91	42
50-59	459	174	38
Total	747	280	37

FIG. 1 Causes of death in men aged 45-64 in England and Wales in 1967. The rates are per million men living.

amples from hundreds of statistical studies. In summary, it appears that, in countries with the highest incidence, coronary heart disease is the cause of death in about 4 of 10 men, and that it accounts for one-quarter of male deaths between the ages of 35 and 44 years.

The Registrar General's 1967 figures for the certified causes of male deaths between the ages of 45 and 64 summarize the present coronary mortality in England and Wales, in comparison with other causes of death (Fig. 1).

Nature of the disease

Mortality figures are less interesting to most of us than the nature of the disease, and it is this that determines the main pattern of the coronary problem.

Atherosclerotic narrowing of the coronary arteries is known to start early in life, usually without any clinical manifestation. In a study of 300 American soldiers, average age 22.1 years, killed in the Korean war, Enos, Holmes, and Beyer (1953) found macroscopic coronary atherosclerosis in 77 per cent of cases, and in 12.3 per cent one or more of the main coronary arteries was narrowed by atheroma to half, or less than half, the original lumen. Subsequently, Mason (1963) collected published studies of the state of the coronary arteries of 275 young men killed accidentally, and found that narrowing by atheroma of one

or more main coronary arteries to one-quarter or less of the original lumen had occurred in 14 per cent between the ages of 20 and 24, and in 32 per cent aged 40 to 49 years.

The usual age of onset of coronary atherosclerosis is unknown, but Osborn (1963) has made extensive histological studies of the coronary arteries from infancy throughout life. He concluded that: 'Most or all of those destined to die from "coronary thrombosis" before their allotted span owe their fate to lesions of early life, not infrequently of infancy.'

Though the histological evidence collected by Osborn may establish the early age at which coronary atheroma can begin, it is probably unwise to give this so sweeping a selective prognostic significance, for, despite Osborn's views, it seems likely that the liability to clinical coronary disease depends to a large extent upon the complication of thrombotic occlusion. The Mayo Clinic workers (Spiekerman *et al.*, 1962) found that, in Rochester, coronary disease was present at death in 3 of 4 adults, yet only 40 per cent of men and 22 per cent of women died from the disease.

Onset of symptomatic phase The way in which asymptomatic coronary disease enters the clinical phase is of considerable practical importance. Practising cardiologists do not come into contact with a considerable proportion of sudden deaths in this condition, and are likely to underestimate the frequency with which this is the first and only manifestation of coronary disease. With this in mind, Kuller, Lilienfeld, and Fisher (1966) studied the natural history of 1030 deaths from 'arteriosclerotic heart disease' in Baltimore residents, aged 40-64, during the year 1964-65. In the 610 deaths in white men aged 40-64, about one-fifth were found dead, half the deaths had occurred within 2 hours, and two-thirds within 24 hours (Table 2). In the whole series only

TABLE 2 Coronary deaths in white men age 40-64

Time of death	No.	Per cent	Cumulative per cent
1 Found dead	115	18.9	18.9
2 Dead within 2 hours	175	28.7	47.6
3 Dead in 2-24 hours	99	16.2	63.8
4 After 24 hours	221	36.2	100
Total	610	100	—

1 + 2 = Total neoplastic mortality in age-group (Baltimore survey).

19 per cent of the coronary deaths occurred after 24 hours in hospital, and one-third of these hospital deaths were in patients admitted for diseases other than coronary heart disease.

Kuller and his colleagues used a complicated definition of sudden death which included an element of unexpectedness in addition to a time interval of less than 24 hours between onset and death. On their definition, 60 per cent of deaths were 'sudden'. Sudden or unexpected death occurred more frequently when there was no previous history of heart disease, for in this group 74 per cent of deaths were 'sudden'. In 229 'initial' coronary attacks in the Framingham study (Dawber, Kannel, and McNamara, 1964), 58 per cent of deaths occurred within the hour and in 70 per cent of fatal cases it was not possible to get the patient to hospital, usually because death occurred so quickly, but in a few cases because atypical symptoms evaded diagnosis.

If sudden death is more common in initial attacks it might be expected to occur more often in the young, but it is not easy to find detailed studies of large numbers of cases in very young men. Yater and his colleagues (1948) have, however, studied 850 cases of coronary disease in American soldiers, age 18-39, in World War II. The mortality was high, 53 per cent (450 of 850) compared with about 30 per cent in most population studies, and 83 per cent of the deaths occurred within 24 hours. In 208 of 450 fatal cases no symptoms were recorded, and in 123 of the remaining 242 no symptoms occurred before the fatal attack. Thus, in 74 per cent (331 of 450) of these deaths there was no history of symptoms before the fatal attack.

The term 'sudden' death is used in many differing interpretations, and, in considering the possibility of reducing the mortality by treatment, the number of deaths within one hour, or 24 hours, is potentially less important than the number who die undiagnosed. This can happen either because there are no symptoms before death, or because the symptoms are too atypical to suggest the diagnosis. There is thus a practical distinction between 'sudden' and 'unexpected' death. Death is usually unexpected if no satisfactory diagnosis has been made, however long the symptoms have lasted; on the other hand, even instantaneous death is not unexpected if it occurs in a person known to have severe coronary disease. Thus death is more likely to be unexpected when it occurs in the first attack, and this is more liable to happen in younger people.

Unexpected death is usually reported to

the coroner in this country, and in these cases a satisfactory clinical diagnosis has usually not been made. This is the part of the mortality which flying squads and intensive care units can scarcely influence. It therefore seemed useful to attempt to assess the proportion of coronary deaths in which a coroner's necropsy is ordered. Such information can be derived from insurance company files, for, in England and Wales, if the coroner orders a necropsy he signs the death certificate. This investigation shows that 47 per cent of all male deaths certified as due to coronary diseases were reported to the coroner (Fig. 2).

FIG. 2 Frequency of coroners' necropsies in 847 deaths from coronary heart disease in insured persons.

This is not surprising in view of the figures already discussed, and it is almost certainly an underestimate of the proportion of sudden (as distinct from 'unexpected') deaths, for in the older age-groups many sudden deaths will be accepted as due to known severe coronary disease, and not reported to the coroner. It is more surprising that there is so much difference between the proportion of coroner's necropsies in the older and the younger age-groups, 76 per cent under age 40 falling progressively to 28 per cent in those over age 70. In the first six decades this is not due to greater tendency to report younger deaths in general, for there is no such tendency in other diseases (Fig. 3). Deaths in which there is a legal obligation to report to the coroner have been excluded from this comparison. In coronary deaths under age 40, the 76 per cent of deaths reported to the coroner is similar to the 74 per cent of sudden and unexpected deaths in new cases of coronary disease in the Baltimore study, and the 70 per cent of fatal cases it was not possible to get to hospital in

FIG. 3 Frequency of coroners' necropsies in deaths from coronary heart disease compared with deaths from other causes.

the Framingham study, but rather less than the 83 per cent of deaths within 24 hours in soldiers under age 40 (Yater and his colleagues, 1948), though some of these deaths were almost certainly not unexpected.

Prognosis of initial myocardial infarction We are now perhaps in a position to consider what happens to those who have their first myocardial infarct. For this purpose morbidity as well as mortality figures must be known, and perhaps the best available information comes from the Framingham study (Dawber *et al.*, 1964) which covers both men and women, age 30-59 at entry to the study. In Table 3 the figures for 229 initial infarcts have been converted to percentages. Of each 100 cases, 42 were not admitted to hospital, and 23 of 33 deaths occurred in this group, including 20 deaths within one hour. In 11 cases the diagnosis was not made at the time but by chance after recovery, usually at routine electrocardiography. The 20 deaths within an hour,

TABLE 3 Mortality of initial myocardial infarction
Percentages from 229 cases (Framingham Study (Dawber *et al.*, 1964))

Not admitted to hospital	42
Total deaths	23
Sudden deaths	20
Undiagnosed at the time	11
74% could not be treated	
Admitted to hospital	58
Died within 3 weeks	10
Mortality within 3 weeks	33%
20 of 33 deaths were sudden	60%

added to 11 undiagnosed cases, account for 74 per cent of cases not admitted, and for 60 per cent of all deaths. The 20 sudden deaths would not ordinarily be picked up in clinical mortality statistics, and the 100 cases would then appear as 80 with 13 deaths, which halves the mortality (33 to 16%). If we assume that the 11 non-fatal cases, unrecognized at the time, would also escape recognition except in a population survey, then the mortality becomes 19 per cent. A considerable part of the pattern of coronary disease normally escapes clinical recognition.

Pathology of heart in sudden death from coronary disease Throughout the studies already discussed there has been some suggestion that in coronary heart disease unexpected death occurs more frequently in the first clinical ischaemic event. If this is so, it may be partly due to a greater liability to sudden death in the earlier than in the advanced stages of coronary heart disease. Some support for this hypothesis comes from a study of the pathology of hearts from cases of sudden death. Unfortunately, in coronary disease the number of vascular and myocardial abnormalities recognized at necropsy depends very largely upon the pathological techniques employed, so it is not possible to compare cases drawn from different sources. This point can, however, be fairly illustrated by a combined series of 30 clinical cases and 50 sudden death cases (reported to the coroner) which we studied simultaneously by identical techniques of coronary injection and extensive serial slice histology of the myocardium (Snow, Jones, and Daber, 1955; Jones, 1969). The pathological differences are summarized in Table 4 and suggest that the number and severity of the vascular and myocardial lesions are much less in the sudden death

TABLE 4 Comparison of pathology of heart in clinical coronary disease and sudden death

	Clinical (30 cases)	Sudden death (50 cases)
Without coronary occlusion	0	36% (18)
Without infarction	0	16% (8)
Without infarction or occlusion	0	12% (6)
		Atheroma and ischaemic fibrosis 4
		Atheroma only 2
Number of infarcts	2.6 per case (78)	1.6 per case (79)
Number of occlusions	1.7 per case (50)	0.8 per case (38)
Infarcts without occlusions	14% (10)	43% (34)

cases. Naturally the suspicion arises that sudden death may have been due to some other cause in some of these cases. It is scarcely ever possible to prove that death is due to coronary disease, but, in these cases, necropsy revealed no other cause, and 48 of the 50 cases had either complete occlusion of a main coronary artery or evidence of ischaemic damage to the myocardium. It is an interesting feature of the cases of sudden death that nearly half the infarcts (43%) occurred without corresponding complete occlusions of a main coronary artery. Others have noted this: Branwood and Montgomery (1956) found no coronary occlusion in 18 of their 26 cases of sudden death though infarction was present in all 26 cases.

Thus statistical and pathological evidence suggests that, in coronary heart disease, unexpected or sudden death occurs more frequently in the earlier stages of the disease and in initial attacks, and the pathological evidence indicates that unexpected death often occurs without complete coronary occlusion, though myocardial infarction is usually detectable histologically.

Changing incidence of coronary heart disease

The salient characteristic of coronary heart disease is the very large part it plays in total mortality at the present time, especially in men from age 35 upwards. This is not seriously disputed, but much more open to argument is the contention that the true mortality from coronary disease has increased in the present century. If this is true, then, as Epstein and Krueger (1969) have pointed out, it must be due to changes in our pattern of living, since genetic characteristics cannot have altered in so short a time. Only if environmental influences responsible for a true change in incidence are identified are preventive measures likely to be available. In fact, our hope of preventing ischaemic heart disease is based principally on the belief that the true incidence has increased for environmental reasons. In any assessment of the nature of the coronary problem, it is therefore mandatory to consider the evidence that exists for a true change of incidence, and the work that suggests that some characteristics of our way of living increase our liability to coronary disease.

Mortality statistics No one is now willing to believe long-term trends shown by statistics based on death certificates in the category of 'arteriosclerotic heart disease' (Fig. 4). Thus, in England and Wales, the enormous increase in deaths due to 'arterio-

FIG. 4 Death rates per million living men aged 55 to 64 in England and Wales.

sclerotic heart disease' is largely offset by the striking decrease in 'degenerative heart disease'. There still seems to be a gradual increase in the combined mortality (Fig. 4), but the factor of better diagnosis has not been taken into account. This is, however, likely to be more important in assessing morbidity than mortality.

From these figures it may be suspected that there was, in this country, a tendency for mortality to fall during and after World War II, not unlike the decreases at this time reported from Norway, Denmark, Finland, The Netherlands, and Germany; these statistics have been critically reviewed by Keys (1963).

There can be no doubt that international mortality statistics were unreliable before 1948 when a more satisfactory international classification of coronary and myocardial disease was introduced. Up to this time, I am happy to agree with my distinguished colleagues, Maurice Campbell (1963), Robb-Smith (1967), and Evan Bedford (1968) when they conclude that there is no satisfactory evidence for an increasing age-specific mortality from coronary disease, though I believe that such statistics are equally unreliable in excluding such an increase.

Some more recent mortality statistics, however, deserve closer attention. World Health Organization (1967) statistics comparing age-specific mortalities in 1955 and 1964 from the ten countries with the highest over-all male coronary mortality rates (I.C.D. 420-422) (Oliver, 1969) are less subject to error, and the averaged figures reveal a disturbing trend (Fig. 5). The figures in different countries are dissimilar but there can be little doubt that a real increase in male age-specific mortality has occurred, at least in some countries and that,

FIG. 5 Percentage increase in male death rates from arteriosclerotic and degenerative heart disease (420-422) in 1955 to 1964 in 10 countries (Scotland, U.S.A., Sweden, England and Wales, Australia, Denmark, Finland, Norway, Canada, and W. Germany) with highest over-all death rates in 420-422 (World Health Organization, 1967).

in those countries in which the increase is greatest, there has been a disproportionate rise in mortality in the younger men. In England and Wales the male mortality has risen 35 per cent in the 45-54 age-group and 50 per cent in the 35-44 age-group. Epstein and Krueger (1969) have pointed out that the lack of correlation between the level of the mortality rates in different countries and the rate of increase militates against the view that increases are fictitious. Thus, the high mortality rate in U.S.A. is associated with only a very small increase between 1955 and 1964 (Fig. 6).

Migration from an area of comparatively

FIG. 6 Per cent increase in coronary heart disease in individual countries (from *Modern Trends in Cardiology, Volume 2*, reproduced by kind permission of Messrs. Butterworth & Co., Ltd.).

low coronary mortality into a population with a higher mortality has been extensively studied (Epstein and Krueger, 1969), and, in general, there is a tendency for the migrant population to move towards the mortality trend of their new environment. There are difficulties in drawing conclusions from such studies, for those who migrate may differ mentally or physically from those who stay at home, and migrants also acquire the diagnostic standards and certification characteristics of their new community.

As Rose and Blackburn (1968) have pointed out, mortality statistics are useful in indicating where the main problems of chronic diseases lie, but their conclusions are, at best, tentative and need testing and extending by more direct studies in population groups. Thus, while mortality studies suggest that environmental factors may play a part in increasing coronary mortality, population studies have done much to confirm and quantitate these factors.

Population studies The results of the Framingham (Dawber *et al.*, 1964) and Albany (Doyle, 1966) studies are too well known to require much discussion, but perhaps it is worth recalling briefly some of the more quantitative aspects of their results (Fig. 7). Apart from non-specific electrocardiographic abnormalities, the most important risk factors have to do with our way of life, especially cigarette smoking and serum cholesterol, in so far as this is influenced by diet. A comparatively small range of cholesterol levels covers a considerable variation in the likelihood of developing coronary disease. The greater increased liability associated with cigarette

FIG. 7 Percentage of men, age 40, developing coronary heart disease in 20 years (Albany study).

FIG. 8 Risk of developing coronary heart disease in 8 years in men aged 30-59 on entry (Framingham study).

smoking appears to be an acute risk, for stopping smoking promptly reduces the liability to that of non-smokers, and the duration of the habit does not affect the risk (Doyle and colleagues, 1964). The amount of physical activity and the degree of psychological stress are factors in our way of life which do not lend themselves to quantitative analysis but, like nicotine, stress mobilizes catecholamines which, in turn, raise free fatty acids in the blood, though the significance of these changes is undetermined (Doyle, 1966). When more than one risk factor is present the cumulative effect is striking (Dawber *et al.*, 1962) (Fig. 8). In the clinical situation it is sometimes comforting to realize that a young man with only one risk factor, such as hypercholesterolaemia, still has a lesser risk of coronary disease than the average in his age-group.

Prevention of coronary heart disease

I have emphasized those features of the natural history of coronary disease that strongly suggest that our principal hope of substantially reducing mortality lies in prevention of the progress of the presymptomatic disease. These features are the development of asymptomatic coronary atheroma early in life, and the large proportion of deaths that occur suddenly or unexpectedly before treatment can be given, often in the earlier stages of the disease and as the initial clinical manifestation.

Several factors known to increase the risk of developing coronary heart disease are potentially treatable; cigarette smoking, a high serum cholesterol, hypertension, considerable obesity, and possibly physical inactivity. There are two groups of persons in whom preventive measures might be used; those who have already had an initial clinical

coronary incident (secondary prevention), and those without clinical disease in whom significant risk factors, or presymptomatic disease, can be recognized by population surveys (primary prevention).

Clinical coronary heart disease Once the initial clinical thrombosis has occurred, it may well be too late to prevent further developments, and a number, equal to half the survivors, have already died. Of the available preventive measures, only stopping cigarette smoking has so far been shown to reduce the frequency of further ischaemic incidents in the myocardium. It may not be unreasonable to lower very high serum cholesterol levels, to treat hypertension, to reduce obesity, and to encourage physical activity, but no proof has yet been adduced that such measures do, in fact, improve the prognosis of survivors from the initial attack.

Presymptomatic diagnosis Oliver's (1968, 1969) recent reviews of the problems of presymptomatic diagnosis emphasize the difficulties inherent in this field. Even if the presence of one or more risk factors is recognized, the majority of these people will not develop clinical coronary disease in the foreseeable future; from this point of view, it is not so relevant that 35 per cent with a risk factor will develop clinical disease in 20 years, as that 65 per cent will not. Indeed, Stamler (1964) has shown that, when four factors (high cholesterol, hypertension, heavy cigarette smoking, and excess weight) are all present simultaneously, less than half (44%) of men will develop clinical coronary disease within 10 years. Epstein (1967) has estimated that, if high serum cholesterol and hypertension are both present, only one-third or one-fourth of men aged 30-39 will develop clinical coronary disease within 10 years, and only one-fifth in the 40-59 age-group.

The second more fundamental objection to mass population screening is that we cannot at present prove that available measures are effective in preventing the disease, except advice to stop cigarette smoking, and this requires no screening. Oliver (1967) reviewed the control of hyperlipidaemia, and concluded that there was no evidence that this modified the prognosis in established coronary disease. Page and Stamler (1968) admitted that it was no more than an opinion that it was worth while to decrease total fat intake and to correct obesity. Control of severe hypertension has, so far, not led to any striking reduction in coronary mortality in treated cases. There is also the possibility that the detection of a

symptomless, often fatal, disease, or the tendency to develop it, could do harm if we have no remedy to offer. There is, of course, good reason to recognize asymptomatic coronary disease in certain groups, such as air-line pilots and express engine-drivers, but in business and professional men and in manual workers profitless recognition of the asymptomatic disease may greatly impair their employability, even if it does not seriously disturb their equanimity. Oliver (1968) has concluded that it is economically and morally indefensible to promote a national survey of this kind until it has been shown that the disease can be controlled.

Preventive trials Though there is no present justification for national screening for risk factors, or widespread attempts to detect presymptomatic disease, it is nevertheless essential to encourage limited controlled preventive trials, both in the established disease and in selected groups screened for significant risk factors. Studies of the effect of controlling risk factors in the established disease are not particularly difficult to undertake, but trials of primary prevention in the presymptomatic phase are both difficult and unwieldy. Several such trials are under way. Stamler (1969) has recently reviewed the first five years of the Chicago programme, and the first seven years of the New York programme have been described by Christakis and his colleagues (1966). Studies in special groups, such as patients in mental hospitals in Finland (Turpeinen and colleagues, 1968), and elderly men in Los Angeles (Dayton and Pearce, 1968) have also been recently reviewed. Stamler (1969) has concluded that all these studies show some decrease of either incidence or mortality as a result of changes in living habits and reduction of serum lipids, but all are small groups and all have a flaw, either a high 'drop-out' rate, or absence of a satisfactory control group, or lack of double-blind design. For these reasons, and also the present short duration of these trials, no firm conclusion on the value of primary prevention can at present be reached. Stamler (1969) believes that it will be another decade before any conclusive result can be expected from primary prevention studies.

Conclusion

I have tried to bring out those facets of the coronary problem, the most important current medical problem, which make it particularly difficult to solve. First, its size, for in countries with the highest incidence it accounts for about 40 per cent of all adult male

deaths. Secondly, the evidence which suggests that the incidence is rising, even in the past decade or so, and that this increased mortality falls especially upon younger men. Third, the nature of the disease itself, with its long asymptomatic phase, starting early in life; its presence in a large proportion of the population at death; the fact that half of all coronary deaths occur unexpectedly, with the disease undiagnosed; and the disquieting feature that in initial attacks there is no opportunity for treatment in 70 per cent of the fatal cases. For these reasons the practising clinicians' view of the top of the coronary 'iceberg' is misleading. Salvage of the survivors, either by treatment in the acute phase or subsequent 'secondary' prevention, can do little to reduce the total mortality. The evidence suggests that some characteristics of our way of life significantly increase our liability to coronary disease, but it may be necessary to start 'primary' preventive measures early in life, and considerable difficulties have been encountered in proving that available measures do, in fact, reduce the morbidity or mortality. It is now quite essential to assess scientifically the value of present preventive measures; to do this it will be necessary to divert considerable economic and medical resources for at least a decade, and much longer if it proves necessary to start prevention in early life.

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